IN THE MATTER OF:

A representation under s25(1) of The Patents Act, 1970 as amended by the Patents (Amendment) Act 2005 ("the Act") and Rule 55 of The Patents Rules, 2003 as amended by the Patents Rules, 2006 ("the Rules") by the Initiative for Medicines, Access & Knowledge (I-MAK) ("the OPPONENT")

And

IN THE MATTER OF:

Indian Application No. 339/MUMNP/2006 by Abbott Laboratories ("the APPLICANT")

STATEMENT OF THE OPPONENT IN REPLY TO THE APPLICANT'S RESPONSE FILED UNDER RULE 55(4)

1. We, the Initiative for Medicines, Access & Knowledge (I-MAK), (the Opponent), reply to the response filed by the Applicant under Rule 55(4) in the present proceedings. It is stated that the present reply deals with certain crucial aspects brought out by the Applicant and such reply ought to be taken on record in the interest of justice and the fair trial of the present opposition.
2. It is stated that on 1 March 2006, the Applicant filed an amendment of its claims for 339/MUMNP/2006 (‘339). On 16 August 2007 the Opponent filed and received confirmation from the Mumbai Patent Office of its representation by way of opposition against ‘339. On 9 January 2008, the Applicant filed its response to the Opponent’s opposition against ‘339.

3. In view of the forthcoming hearing on 23 February 2009, this statement re-affirms the grounds of opposition filed on 16 August 2007. In light of the Applicant altering its claims, which were not made available to the Opponent at the time of filing its opposition, this statement addresses these amendments. More importantly, this statement provides compelling evidence that responds to the arguments and evidence put forward by the Applicant and why ‘339 should not be granted. The Opponent respectfully submits that as a public officer being the custodian of the public interest, the Honourable Controller ought to take on record the present reply and consider the same during the adjudication of the present opposition. The Opponent also believes that this reply ought to form part of the records of the present opposition so as to ensure a fair adjudication that complies with the principles of natural justice.

4. The Applicant has unnecessarily repeated many of its arguments in no logical order and under different guises throughout its statement so as to confuse the issues at hand. Therefore, the format of this statement is not designed to respond to the Applicant paragraph-by-paragraph, but only to each particular argument (providing relevant page and paragraph numbers).
5. On page 2, Paragraph B, titled 'Preliminary Objections' the Applicant asserts that the Opponent is required under Rule 55(1) of the Rules to file "substantial" evidence in the form of technical or expert statements, and the failure to do so warrants the dismissal of the representation of opposition. This assertion by the Applicant, which the Opponent is confident the Honourable Controller is fully aware of, is pure legal chicanery and fiction. It is stated that under Rule 55(1) the filing of evidence is optional. However without prejudice to such statement it is stated that neither Rule 55(1) of the Rules, any other provision in the Act, or rule of evidence in civil procedure requires that evidence can only be in the form of expert declarations. The Opponent states that the prior art relied upon by the Opponent is itself evidence in support of its allegations under the various grounds. The Opponent, by submitting with its statement of opposition, Exhibits 1-15, has provided more than substantial evidence upon which this patent office can base its decision in this matter.

6. Under the heading 'Reply on Merits' on pages 2, 3 and 4 of the Applicant's response, the Applicant resorts to making *ad hominem* attacks in an attempt to discredit the Opponent and divert attention away from the evidence the Opponent has submitted. The Opponent would like to reply in particular to the following assertions by the Applicant, and respectfully prays to the Honourable Controller to dismiss the Applicant's reply on the merits:

6.1 The Applicant claims to be unaware of the constitution of the Initiative for Medicines, Access & Knowledge (I-MAK). The objective of the Opponent was stated clearly in its statement of opposition in paragraph 1 as follows: "I-
MAK consists of lawyers and scientists working to protect the public domain against undeserved patents to ensure that patents do not act as a barrier to research and restrict the public’s access to affordable medicines.” Indeed, our website traffic monitor shows that the Applicant and its attorneys have regularly visited our website (www.i-mak.org) and is well aware that the Opponent is a not-for-profit U.S. §501c3 organisation, organised and operated exclusively for charitable purposes. Section 501c3 organisations in the U.S. are ones in which no part of the net earnings of the organisation inure to the benefit of any private individual. Therefore, it is clear to the Applicant what the constitution of the Opponent is. For the Applicant to say otherwise is to mislead and unnecessarily expend the time of this patent office. The wrongful denials clearly go to show the mala fide conduct of the Applicant.

6.2 The Applicant claims that the Opponent has “misused the provisions of s25(1) of the Act as a tool to defeat, stall and delay the grant of patents by filing frivolous pre-grant oppositions in the guise of public interest.” The Applicant goes on to state “the Government has taken several measures while drafting the patent legislation to prevent patent abuse.” It seems the Applicant is conveniently unaware of the legislative intent of Section 25(1). While Parliament had every opportunity to remove pre-grant opposition procedure during the passing of the Patent (Amendment) Bill, it decided to have both pre-grant and post-grant opposition mechanisms unlike most other countries, with a purpose that indisputably was to ensure that bad patents do not get granted, and if granted are revoked. Moreover, the wording of Section 25(1) clearly states that “any person” may file in writing a representation of
opposition to the grant of a patent. This was done to ensure wider public participation in India’s patent system so as to strengthen the patent office in its role. The Opponent is simply exercising its legitimate right where it believes a patent application is not in compliance with legal requirements for patentability, and where such a non-meritorious patent, if granted, will negatively impact the public interest. The Opponent is acting in the interest of the public at large and not for its own gains.

6.3 The Applicant states that the Opponent “has a history since their inception to stall the grant of patents for ‘all’ pharmaceutical patent applications globally directly or indirectly related to HIV treatment” and that the Opponent “is against the grant of patents” or any “anti-retro-viral drug”. The Opponent wishes to place on record that since its inception in 2006, 339 is the first and only application to date that I-MAK has opposed in India or filed an observation against in Europe. The Opponent has provided technical assistance to Indian HIV patient groups in seven other pre-grant oppositions, which only relate to three other HIV products. Indeed, two of these oppositions have helped to successfully weed out unmerited patent applications. Out of the more than hundred HIV related patents and some 9000 pharmaceutical product patents that were filed in the mailbox, it is clearly obvious the Opponent only involves itself selectively with the pre-grant opposition procedure where it believes there is a case of an unmerited patent that would not be in the public and scientific community’s interest. For the Applicant to suggest that the Opponent is ‘against the grant of all patents’ or any ‘anti-retro-viral drug’ simply shows the desperate nature of the
Applicant’s arguments.

6.4 The Applicant contends that ‘drug pricing and drug availability do not come within the ambit of patents.’ The Applicant also alleges that the Opponent does not fully understand the inherent nature of the patent system and that patents are granted to provide exclusivity to innovators. The Opponent is fully aware of the purpose of the patent system. The patent system was founded on providing incentives and rewards, by way of a period of exclusivity, to genuine inventions. However, what the Applicant has aptly forgotten to mention is that patent exclusivity is granted only for genuine inventions that meet the particular requirements of a country’s law, and not merely because an applicant has spent time and money on research and development using existing technologies that do not result in any new knowledge. Granting unmerited exclusive rights to one party does play a role in drug pricing and availability as it prevents legitimate competition in the marketplace, the costs of which are unnecessarily borne by consumers and government health care programmes, such as India’s National AIDS Control Programme. For the Applicant to state otherwise is simply an attempt to deceive this patent office.

7. In short, the Applicant has throughout its ‘Reply on Merits’ either used selective extracts from the Opponent’s statement of opposition or simply created fiction in an attempt to discredit the Opponent. The Opponent would like this patent office to note that its interests lie solely in strengthening the patent system using legally available tools. To that end the Applicant’s ad hominem attacks should be ignored.
Analysis of the Amended Claims

8. It is stated that the Amendments have not been carried out in the manner prescribed under law. The Applicant is required to make an application under Section 57(2) giving full particulars of the reason for which the application for amendment is made. In the present case, the Opponent is not aware of any application made on Form 12, including the furnishing of full particulars of the reasons, which are statutory mandates and cannot be ignored.

9. Without prejudice to the objection of the Opponent to the admissibility of the amended claims, for the purpose of understanding the Applicant's arguments, the Opponent deems it necessary to first summarise the key amended claims for '339. They may be summarised as follows:

   a) Claim 1 relates to a solid 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 ritonavir, and each of said at least one pharmaceutically acceptable water-soluble polymer has a Tg of at least 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.

Therefore, Claim 1 claims at least one HIV protease inhibitor. In this claim
the Applicant identifies ritonavir as the relevant HIV protease inhibitor. However, the wording 'at least one HIV protease inhibitor' clearly leaves scope for the Applicant to claim additional protease inhibitors alongside ritonavir.

b) Claims 2 and 3 are dependent claims of claim 1, claiming a solid dispersion that is a glassy or solid solution and where the surfactant has an HLB value of from about 4 to about 10.

c) Claim 4 covers the pharmaceutical composition in claim 1 wherein said at least one pharmaceutically acceptable surfactant is a combination of at least one pharmaceutically acceptable surfactant having an HLB value from about 4 to about 10 and at least one further pharmaceutically acceptable surfactant.

The claim covers the pharmaceutical composition of claim 1 where at least one surfactant in the combination of surfactants has an HLB value from about 4 to about 10.

d) Claim 5 claims the surfactant sorbitan fatty acid ester within the pharmaceutical composition of claim 1.

e) Claim 6 covers the pharmaceutical composition as claimed in 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.

Claim 6 fails to include the weight ratio of the water-soluble polymer and is therefore an invalid claim. This is because the Applicant is relying on the weight ratio for the water-soluble polymer of 50-85% provided in claim 1. If the higher figure of each of the weight ratios given in claim 6 are taken i.e. 30% HIV protease inhibitor, 20% surfactant and 15% additives, the formulation would not work.

f) Claim 7 covers the pharmaceutical composition in claim 1 wherein said at least one protease inhibitor further includes lopinavir.

It is clear from claim 7, therefore, that the Applicant is also claiming the protease inhibitor lopinavir with ritonavir as claimed in claim 1.

g) Claim 8 claims the pharmaceutical composition of claim 1 wherein the water soluble polymer has a Tg from about 80 to about 180°C

h) Claim 9 covers the pharmaceutical composition of claim 1 wherein the water-soluble polymer is a homopolymer or copolymer of N-vinyl pyrrolidone. Claim 10 also claims the copolymer of N-vinyl pyrrolidone.

The Applicant has repeated the claim for a copolymer of N-vinyl
pyrrolidone in claim 10 and should, therefore, be requested to delete this item.

i) Claim 11 claims the composition of claim 1 and at least one additive selected from flow regulators, disintegrants, bulking agents and lubricants.

This is an overly broad claim and not permitted within the provisions of the Act. Nowhere in the subsequent claims does the Applicant narrow its claims with respect to the types of flow regulators, disintegrants, bulking agents or lubricants that may be used. This is despite the Applicant providing a list of suitable additives on page 12 of 339.

j) Claim 12 covers 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 15% by weight additives.

With the exception of the words 'solid dosage form' (which is of no additional significance) claim 12 repeats Claim 6. Therefore, claim 12 should not be permitted.

k) Claims 13 and 14 claim the pharmaceutical composition of claim 1, and at least one water-soluble polymer and surfactant selected from a broad list.
339 fails to provide examples for each of the water-soluble polymers within the specification. Therefore, these claims are not supported, as only a very limited number of surfactants and water-soluble polymers have been exemplified.

l) Claims 15 and 16 claim the pharmaceutical compositions of claims 13 and 14, wherein said water-soluble polymers are a homopolymer, copolymer of N-vinyl pyrrolidone or copovidone and the surfactant is a sorbitan fatty acid ester or sorbitan monopalmitate.

m) Claim 17 covers 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 from about 5 to about 30% by weight of the composition, and said surfactant is present from about 2% to about 20% by weight of the composition.

The comments made above with respect to claim 6 equally apply here.

n) Claims 18 through 20 cover the pharmaceutical composition of claim 17 wherein the water-soluble polymer is a copolymer of N-Vinyl pyrrolidone and vinyl acetate or copovidone and the surfactant is sorbitan monopalmitate.
o) Claim 21 covers the pharmaceutical composition of claim 17 wherein the said at least one HIV protease inhibitor comprises lopinavir.

p) Claim 22 covers the pharmaceutical composition of claim 20 wherein the said at least one HIV protease inhibitor further comprises lopinavir.

q) Claims 23 and 24 cover methods for preparing the composition of claim 1.

r) Claim 25 covers a pharmaceutical composition comprising a solid dispersion of at least one HIV protease inhibitor (wherein the said HIV protease inhibitor is ritonavir) in at least one pharmaceutically acceptable water soluble polymer and acceptable surfactant prepared by a process according to claim 23.

This claim serves to be broader than claim 1, upon which all the other claims are dependent. Accordingly this claim is invalid.

10. It is clear from the amended claims that the Applicant is claiming a solid pharmaceutical dosage composition, in the form of a solid dispersion, comprising at least one HIV protease inhibitor, including ritonavir, and ritonavir and lopinavir in at least one pharmaceutically acceptable water soluble polymer (with a Tg of at least 50°C) and at least one pharmaceutically acceptable surfactant with a HLB value from about 4 to about 10. The above fact is confirmed by the Applicant in its statement on page 9, paragraph 4 where it is stated "Another protease inhibitor, for instance lopinavir, can be co-formulated with ritonavir in a
solid dispersion of the present invention.' Therefore, the Opponent would like to highlight in advance that any statements by the Applicant that argue that ritonavir and lopinavir together do not form part of their application, are incorrect and
misleading.

Amended claims 1-25 are not patentable under Sections 25(1)(f) and 3(d) of the Act

Applicant has illogically argued that Section 3(d) does not apply to '339:

The Applicant has argued repeatedly in its statement that Section 3(d) does not apply to '339 for a variety of reasons. The Opponent will deal with each of these in turn.

11. The first of these arguments is that '339 is a novel composition that has not been disclosed in prior art, and '339 is not a known combination (see page 11 of the Applicant's statement in response to paragraph 12 of the Opponent's statement). Section 3(d) clearly states 'a new form of a known substance'. The explanation to Section 3(d) confirms that 'combinations of known substance shall be considered to be the same substance.' '339 is a new form, i.e. a combination, of known substances. '339 is clearly a combination of known substances in a formulation. The known substances are ritonavir, lopinavir (as confirmed by the Applicant in '339 on page 4, lines 16-28), water-soluble polymers such as polyvinylpyrrolidone (PVP), and various general additives. PVPs, surfactants and additives have been used to formulate compounds for decades and are clearly known substances. To that end, the Applicant's arguments that Section 3(d) does
not apply to '339 are simply fanciful and should be dismissed outright.

12. The second issue raised under this head by the Applicant is the nonsensical argument that '339 is either a different substance or a new substance compared to the known substances, because its components are functionally interrelated in novel and inventive ways (see page 13, paragraph 2 and page 15, paragraph 3 of the Applicant's response). The Applicant continues its attempt to substantiate this meaningless argument (see pages 15 paragraph 5 through page 16 paragraph 1 of the Applicant's response), by comparing '339 to any new patentable HIV compounds that are mere combinations of known atoms. For the reasons stated in the preceding paragraph, '339 is a combination of known substances, and is definitively not a new compound as suggested by the Applicant. The Opponent draws to this patent office's attention to the fact that no expert affidavit or technical document has been included to substantiate the Applicant's argument that '339 is a new compound akin to “H, C, N, S or O”. The Applicant's wishful thinking would not stand up to any scientific community's scrutiny.

13. The Opponent reiterates that both ritonavir and lopinavir, the named protease inhibitors covered by '339, are known substances. PVPs, surfactants and other additives have been known for decades. Such known substances are squarely covered within the ambit of Section 3(d) unless their combination in '339 can overcome the requirement of enhancement of efficacy over the known substance. The Opponent addresses this issue below.
Applicant has falsely argued that the soft-gel capsule (WO 00/74677) is not the proper comparison with ‘339.

14. It has already been made clear in the Opponent’s statement and paragraph 11 above that the compounds ritonavir and lopinavir are known substances that have been formulated in various compositions. The Opponent has also identified in paragraph 12 of its representation the relevant known form for the purpose of making a Section 3(d) enquiry: WO 00/74677 (‘677), Exhibit 3. ‘677 is the relevant known form for the purpose of a Section 3(d) enquiry that requires an Applicant to show therapeutic efficacy. This is because ‘677 covers the existing formulation of the known substance ritonavir in a soft-gel capsule (SGC) (marketed as Nervir®), and the substances ritonavir and lopinavir in a SGC (marketed as Kaletra®), that are currently clinically prescribed and marketed to patients globally. Claims 1 and 10 of ‘677 confirm this. The SGC’s are the only known forms against which therapeutic efficacy can be measured. Indeed, as shown in Exhibit 7 in the Opponent’s representation and in further exhibits attached below, ‘677 covers the very known forms that the Applicant also measures ‘339 against in order to assert its claimed advantages.

The Applicant has throughout its statement repeatedly attempted to avoid this comparison in a number of different ways (see for example page 12, paragraph 6, page 16, paragraph 2, page 17-18, paragraph 5 and page 22, paragraph 3 of the Applicant’s statement). The Applicant’s arguments may be summarised as follows:
That '339 does not claim 'ritonavir or lopinavir. Nor does it claim a combination of ritonavir and lopinavir.' (page 12, paragraph 6 of the Applicant's statement).

The Applicant then purports that the proper comparison for '339 be against a mechanical mixture of ritonavir, the water-soluble polymer(s) and surfactants. This, the Applicant claims, is because the composition of '339 has significantly improved efficacy over the mere mechanical mixture of the individual ingredients, which do not significantly improve ritonavir's solubility.

15. These suggestions by the Applicant do not hold up for the simple fact that Section 3(d) requires the new form to show an enhancement of efficacy (therapeutic) over the existing efficacy of a known substance. '677 is the known substance for which there is known efficacy and, therefore, is the relevant point of comparison for this purpose of Section 3(d). If this patent office were to accept the Applicant's arguments, it would be a gross misapplication of Section 3(d) and would render the provision defunct. When an Applicant, like the one in this case, holds a patent cluster around the substances ritonavir and lopinavir, it would open the door to applicant's hand selecting a particular earlier patent or known form that has little or no efficacy in order to obtain a patent. This was not the intended purpose that Parliament had for Section 3(d) and should not be permitted in this case.

16. For the Applicant to argue that '339 does not claim ritonavir, lopinavir, or a combination of lopinavir and ritonavir is simply an attempt to deceive this patent office in order to avoid a comparison with '677. Indeed, the Applicant has throughout its statement made inconsistent references as to which of these protease inhibitors the '339 patent includes. As already demonstrated in paragraph
5 of this statement, claim 1 of '339 covers 'at least' one HIV protease inhibitor and then specifically mentions ritonavir. However, the use of the words 'at least' leaves the claim broad enough to include other HIV protease inhibitors. This the Applicant does in claim 7, as well as in claims 21 and 22, by naming lopinavir. In view of this '339 covers ritonavir, and ritonavir and lopinavir together, which are also claimed in '677.

17. It should also be noted here, nowhere in '339 does the Applicant exemplify the formulation of any other protease inhibitor other than ritonavir and lopinavir. To that end this patent office should dismiss the Applicant's claims which are overly broad in scope as compared to the description and sufficiency of the '339 specification.

18. The Opponent has established above that that the subject matter of '339 is a new form of a known substance that falls within the ground of Section 3(d). The Opponent has also established that '677 is the relevant known substance. Accordingly, the Applicant must show '339 provides an enhancement of efficacy over the known efficacy of '677. In response to the Opponent's statement, the Applicant has provided some 15 pages of arguments, in no logical order, attempting every conceivable argument to establish that '339 provides an increase in efficacy so as to escape the requirements of Section 3(d). For purpose of saving this patent office the time and effort of attempting to extract the various arguments put forward by the Applicant, the Opponent distils the key issues and its response below.
Applicant has wrongly contended that efficacy does not need to be therapeutic.

19. The Applicant contends that the Act does not define the term efficacy to mean only pharmacological and therapeutic efficacy (see page 18, paragraph 1 of the Applicant's response). The Applicant, in an attempt to improperly broaden the meaning of efficacy to benefit its application, argues that the term efficacy can include both therapeutic and non-therapeutic benefits, e.g., stability, better patient compliance, economic efficacy, and other factors. The Opponent refers this patent office and the Applicant back to Exhibit 5 (Novartis AG v Union of India W.P Nos. 24759 of 2006 and 24760 of 2006) of the Opponent's statement. To reiterate, the decision of the High Court of Madras found that efficacy should be interpreted as follows:

"The position therefore is, if the discovery of a new form of a known substance must be treated as an invention, then the patent applicant should show that the substance so discovered has a better therapeutic effect. Dorland's Medical Dictionary defines the expression 'efficacy' in the field of pharmacology as the ability of a drug to produce the desired therapeutic effect, and efficacy is independent of potency of the drug. Dictionary meaning of Therapeutic is healing of disease - having a good effect on the body. Going by the meaning for the word efficacy and therapeutic extracted above, what the patent applicant is expected to show is, how effective the new discovery made would be in healing a disease/having a good effect on the body?"
20. The decision of the Madras High Court removes any doubt as to how efficacy is to be interpreted with respect to pharmaceutical discoveries. The Applicant's suggestion that non-therapeutic efficacy (such as economic efficacy, improved stability, solubility characteristics and better patient compliance) meet the requirements of Section 3(d) is clearly incorrect. The Opponent would like the Honourable Controller to note that the Applicant makes the admission (page 18, paragraph I of the Applicant's statement) that improved stability, solubility and better patient compliance do not amount to therapeutic efficacy. This admission by the Applicant confirms that the advantages of stability and better patient compliance claimed for '339 do not meet the Section 3(d) requirements and the application should therefore be rejected. The Opponent substantiates these reasons in more detail below.

Applicant's has argued that '339 differs significantly from '677 with respect to properties such as stability, resistance against recrystallisation or degradation of the active ingredient. Applicant's argument is flawed in maintaining that these characteristics, which are related to storage conditions, directly manifest so as to enhance the bioavailability and therefore the therapeutic efficacy of the product.

21. The Applicant has argued that '339 differs significantly from '677 with respect to properties such as stability. This increased stability is claimed to provide resistance against recrystallisation or decomposition of the active ingredient, ritonavir. As already highlighted by the Opponent above, stability does not equate to therapeutic efficacy for the purpose of overcoming Section 3(d). The effect of stability to prevent degradation of the active ingredient ritonavir does not
change the therapeutic activity of ritonavir itself.

22. In view of the above reasoning, the arguments put forward by the Applicant relating to improved stability and the lack of degradation of the '339 formulation do not translate to an improvement in the therapeutic content or capacity of the same amount of ritonavir, or ritonavir and lopinavir for the purpose of Section 3(d). Therefore, the therapeutic contents of ritonavir, or ritonavir and lopinavir remain the same in '339 as in '677, and are not patentable under Section 3(d).

23. In order to support its argument of improved stability, the Applicant has advanced the argument that according to the Explanation to Section 3(d), '339 only has to show that it differs significantly with respect to properties. However, the Applicant appears to be in conflict with itself as to whether the Explanation to Section 3(d) is merely an aid for interpreting the provision (see page 11, paragraph 4 of the Applicant’s statement) or to be given heightened importance when self-serving (see page 17, paragraph 3 of the Applicant’s statement). The Opponent’s overall understanding of the Applicant’s self-contradicting response is that the Applicant wishes to argue that the '339 and '677 are significantly different with respect to properties. The Opponent asserts here that the difference in properties claimed by the Applicant relate to stability, which is merely a physical property and not the actual therapeutic effect of ritonavir. It is stated that the alleged improvements in physical property, which do not make any change in the therapeutic efficacy of the compound itself as compared to the known form, do not qualify the requirement under Section 3(d).
In view of the above, the Applicant's arguments with respect to improvement in properties relating to stability and reduced degradation are not sufficient to overcome the Section 3(d) requirement.

24. The Opponent emphasises that changed storage conditions do not constitute therapeutic efficacy. The lack of refrigeration required for the tablet does not translate into improved therapeutic outcomes for the patient. This is merely a method of storage and cannot be considered patentable.

The Applicant has argued that 339 achieves better stability than the SGC in 677. The Applicant has claimed that in narrowly selected conditions, ritonavir degrades less in the new tablet than in the known SGC. While this may be true in the extremely narrow conditions selected by the Applicant, some basic truths must be set out here. First, ritonavir is currently being prescribed globally and the stability issues are not as dire as Applicant has sought to portray here. If stability were indeed such a serious issue, patients all over the world would not be prescribed the drug at this moment. The SGC, under basic storage conditions, is stable as per its product specifications. To suggest otherwise is to imply that thousands of patients taking the capsule form worldwide are currently at risk; we do not think that the Applicant wishes to imply that its previous dosage form was a risk for patients to take. Secondly, stability is nothing more than product quality, and does not change the therapeutic character of the active ingredient ritonavir.

The stability of 339 is analyzed under very narrow conditions; in extraordinarily hot climates, in certain months, for certain periods of time, under selected
scenarios without refrigeration. The intent of Section 3(d) was never to grant patents on new forms of known substances that demonstrated non-therapeutic benefits under varying temperature and timing scenarios. Such benefits, which are certainly not efficacy, are fleeting and do not meet the legal standard.

25. The Opponent notes that the Applicant has also argued that the enhanced stability of ‘339 allows for less degradation of ritonavir, which improves the bioavailability and therapeutic effect of ‘339 over ‘677. The Opponent now addresses the merits of this argument. On page 19, paragraph 3, the Applicant makes a fanciful claim that ritonavir in ‘339 has significantly different bioavailability than ‘677 under certain storage conditions. Indeed, throughout its response, the Applicant has attempted to mislead the Honourable Controller by claiming increased bioavailability under different storage and food conditions. However, absolutely no data is provided by the Applicant to back up the claim that ‘339 tablet demonstrates increased bioavailability over ‘677 capsule based on storage conditions. The Applicant should not contend that the two different formulations of these drugs differ in safety, stability or bioavailability when used as instructed. To do so amounts to an admission by the Applicant that the past and current marketing of the SGC was putting patients at risk. If the Applicant’s best argument is that the ‘677 capsule, when stored under inappropriate and contraindicated conditions, in exceedingly hot temperatures during specific months of the year, is less stable than the ‘339 tablet, causing ritonavir to degrade and be less bioavailable, than the Opponent respectfully rests its case.
The Applicant’s position that a difference in food intake leads to an increase in bioavailability, which may result in an improvement of efficacy, cannot be maintained and should be dismissed.

26. Without prejudice to the above, the Opponent will now address the Applicant’s argument that a difference in food intake between ‘677 and ‘339 results in an increase of bioavailability and may therefore increase efficacy. The Opponent would like to bring to the Honourable Controller’s attention that the Applicant is selectively disclosing information and is not providing the full picture with respect to the claimed efficacy of ‘339. The bottom line, as the Opponent will prove below, is that the subject matter covered by ‘339 and ‘677 are bioequivalent. By definition, if the products are equivalent, there is no difference in efficacy. Since the Applicant has submitted 161 pages of annexeure, most of which are irrelevant for this patent examination, we call out and explicitly state the key arguments for the sake of clarity. We will demonstrate there is no difference in efficacy between ‘677 and ‘339 formulations for the following known substances:

- Ritonavir
- Ritonavir and Lopinavir under meal conditions; and
- Ritonavir and Lopinavir under fasting conditions.

27. The Opponent has already demonstrated through Exhibit 7 in its representation the Applicant’s admission that ‘339 and the SGC formulation in ‘677 are
bioequivalent. However, in an attempt to counter the Opponent's evidence, the Applicant has attempted to confuse the Honourable Controller by providing evidence that conflates the which product its studies and arguments are referring to.

28. In response to the Applicant's evidence, we first focus on the comparison between the ritonavir tablet ('339) and the ritonavir SGC ('677). The Opponent would like to draw the Honourable Controller's attention to two additional documents that substantiate the Opponent's claims that the Applicant has promoted that its '339 product is bioequivalent to its '677 product. The Opponent attaches Exhibit A, *A Comparison of the Single Dose Bioavailability of a Ritonavir Tablet Formulation Relative to the Ritonavir Soft Gelatin Capsule in Healthy Adult Subjects*, J Ng et al, Abbott Laboratories, XVII International Aids Conference, 3-8 August 2008, Mexico City and Exhibit B, *Press Release: Abbott Study Shows Investigational Heat-Stable Norvir® Tablet Provides Similar Drug Levels to Current Norvir Capsule*, Abbott Laboratories, 7 August 2008. We reiterate here that these exhibits refer to ritonavir alone, which is marketed as Norvir®.

29. Exhibit A, provides a single-dose study comparing the '339 tablet of ritonavir to the '677 SGC of ritonavir. In its conclusion, the Applicant states "Ritonavir AUC after administration of the pilot tablet formulation was bioequivalent to the marketed SGC." This is reinforced by Exhibit B, which states that "...investigational Norvir® (ritonavir) tablet and the current soft-gelatin capsule provide similar levels of drug in the blood" and "The ritonavir tablet demonstrates similar bioavailability to the current soft-gelatin capsule, and was
Exhibit A shows a marginal difference in ritonavir AUC and Cmax, respectively, of 12 and 21%. By the Applicant’s own admission, this falls within the range of bioequivalence. More importantly, such a difference does not equate with a difference in therapeutic effectiveness, must less a significant difference. The Opponent would also like to bring to the Honourable Controller’s attention the US Food and Drug Administration’s (US FDA) Application Number: 21-906 Clinical Pharmacology/Biopharmaceutics Review(s), attached as Exhibit C. In Table 2, page 4 (Exhibit page 59), Historical Comparison of Lopinavir and Ritonavir Pharmacokinetics after 400/100 mg BID in Healthy Subjects Following a Moderate-Fat Meal, the data clearly demonstrates that there is virtually no difference in Ritonavir AUC or Cmax between the ‘677 SGC and the ‘339 tablet. Indeed, the fact that regulatory authorities (who are the global experts on such matters) have not requested that the Applicant conduct further clinical trials confirms that there is no difference in therapeutic efficacy, never mind a significance difference in efficacy.

These admissions by the Applicant and the indisputable evidence of the US FDA demonstrate that claim 1 of ‘339, which consists of ritonavir alone, is no more efficacious than ritonavir as formulated in ‘677. Therefore, claim 1 and its dependant claims should be refused under Section 3(d).

30. ‘339 also claims the known substances ritonavir and lopinavir (see claim 7 of the amended claims). The Applicant claims efficacy pertaining to lopinavir and
ritonavir under meal conditions. Relying on Chiu’s declaration (pages 3 of 4), the Applicant claims that ‘339 (when tested as ritonavir and lopinavir) demonstrates increased bioavailability over ‘677 (ritonavir and lopinavir) under a specific set of conditions which increases the efficacy of the product. The Applicant has, however, omitted two critical pieces of information in order to mislead the Indian Patent Office. First, in Table 2, page 4 of Exhibit C (Exhibit page 59), the data clearly demonstrates that there is virtually no difference in Ritonavir or Lopinavir AUC or Cmax between the ‘677 SGC and the ‘339 tablet. Second, this fleeting increase in bioavailability, which does not constitute therapeutic efficacy, is present only in a single-dose test. This means that when administered once to a patient with HIV, a marginal increase in bioavailability (but which is still within the bioequivalence range) is visible. However, as noted by the US Food and Drug Administration (US FDA) in Exhibit C, this small difference in bioavailability becomes virtually non-existent upon repeat dosing. Page 2, paragraph 1.3 of the US FDA report states:

"Single dose BE studies indicate that the to-be-marketed tablet formulation is about 20% more bioavailable than the currently marketed capsules under non-fasting conditions. However, the results from a cross-study comparison indicate that the steady-state pharmacokinetics of lopinavir and ritonavir after administration of lopinavir/ritonavir 400/100 mg BID as the to-be-marketed tablet formulation were similar to that seen in previous multiple-dose studies in healthy subjects using SGC formulations."

The reality is that people living with HIV require multiple dosing of antiretroviral
therapy for life, not a single dose. A scenario where this drug will be used with only a one-off dose is implausible. It is incomprehensible as to how the Applicant believes that showing a single-dose study under a narrow set of conditions can meet the efficacy requirement under Section 3(d). According to Exhibit C, upon multiple dosing of the tablet in '339, any marginal difference in bioavailability virtually disappears under non-fasting conditions according to Exhibit C. Under proper conditions where the patient takes the drug more than once, any bioavailability is similar to that seen with the SGC of lopinavir and ritonavir. Put another way, the '339 tablet for ritonavir and lopinavir is bioequivalent to the '677 SGC.

This is proven beyond any question by the Applicant's own practices. The daily dosage (and frequency) of ritonavir taken is always identical between the SGC and the tablets. The daily dose (and frequency) of lopinavir/ritonavir is also always the same between the SGC and the tablets. That the Applicant is effectively "cherry-picking" the data it wishes to submit to the Indian Patent Office in order to surmount the requirement of Section 3(d) and obtain an exclusive right is deplorable. We present the question to the Honourable Controller -- which statements of the applicant should be believed? Are we to believe the representations made to the U.S. FDA, the European Medicines Authority and other national/international regulatory agencies, that these products are equivalent and therefore do not require additional testing? Or are we to believe the statements to the Indian Patent Office that these products are more efficacious? New pharmaceutical formulations that contain active ingredients that are already approved (as these clearly do) are either equivalent or non-equivalent.
The applicant clearly is willing to represent either of these mutually exclusive statements, depending on the audience and whether advantage is to be gained. The Opponent trusts that Honorable Controller will recognise the facts presented and refuse the application.

31. In addition to the above arguments, the Applicant feebly makes one last attempt at meeting the Section 3(d) efficacy standards under this head. This the Applicant does by claiming that when a patient does not take food with the '677 SGC, there will be a bioavailability difference with a patient taking the '339 tablet. This argument has no merit for the purpose of overcoming Section 3(d) for a number of reasons. First, a person who takes the '677 capsule as prescribed will have the same therapeutic effect as someone who takes the '339 tablet. Second, food effect is about convenience, not about therapeutic effectiveness. Third, there is absolutely no difference in efficacy between these products, which is why patients across the world will be switched in 2009 from the '677 capsule to the '339 tablet without the Applicant being required to do additional clinical trials. This is confirmed by the fact that the Applicant has not put forth any evidence to the contrary. Fourth, and without prejudice to the above, patients would never be prescribed just a single dose of an ARV, and the applicant has failed to demonstrate that there is a bioavailability or efficacy difference with multiple doses between '339 and '677 even under fasting conditions. Fifth, this data shows, at best, that a comparison of administration and methods of treatment are being used by the Applicant in order to obtain a patent. Conditions of administration are unpatentable per se, as are methods of treatment.
Applicant has incorrectly attempted to claim efficacy of ritonavir, or ritonavir and lopinavir in '339, through pill burden, methods of storage improving potency or reduced pharmacokinetic variability. Applicant has not met the Section 3(d) standard.

32. The '339 formulation of ritonavir, or ritonavir and lopinavir has no improved therapeutic efficacy over the formulation and known form that is '677. In its attempts to prove that '339 shows an enhancement of efficacy over '677, the applicant has resorted to claiming reduced pill burden, storage conditions resulting in potency, and decreasing pharmacokinetic variability. We will address each of these in turn.

33. Reduced pill burden does not constitute therapeutic efficacy. As noted above and in the Opposition, therapeutic efficacy is clearly defined in Novartis as, *inter alia*, the ability of a drug to produce the desired therapeutic effect. Reducing the number of pills a patient takes in a day results in the same clinical outcome and relates more to use than therapeutic effect. To reiterate the argument advanced in the Opponent’s opposition, therapeutic efficacy must demonstrate a response or effect in the human body.

34. The Applicant also contends that new storage conditions can lead to more potency. Potency does not amount to therapeutic efficacy. Efficacy in clinical terms is also distinguished from potency. Potency is the concentration or dose necessary to produce 50% of a drug’s maximal effect. Efficacy, also termed
maximal efficacy in this context, refers to the drug's mode of interacting with receptors, with the goal of achieving a maximum positive therapeutic endpoint. The clinical effectiveness of a drug depends not on potency but on efficacy. Potency is important for drug dosage determinations but is unimportant for clinical purposes.

35. The Applicant has also indicated that a modest increase in exposures to levels of lopinavir will result for HIV patients, from substitution of the tablet for the SGC. It is implied that these additional exposures may result in a better efficacy, which can only be defined as suppression of viral load. The Applicant has presented no data to support this claim. The Applicant's data that would most closely support any hint of enhanced efficacy bear upon pharmacokinetic variability of lopinavir levels, but these are only a comparison made upon single dosing. Decreased pharmacokinetic variability after single-dose treatment of a drug does not equate with improved therapeutic efficacy. Pharmacokinetic variability is defined by a number of factors including metabolism, elimination and distribution. All of these are part of a pharmacokinetic profile. Therapeutic efficacy is not determined by a single pharmacokinetic parameter. For HIV, it is determined by reduced viral load of the HIV virus itself (copies of HIV RNA/mL). The Opponent has already shown above that the steady-state pharmacokinetic profiles of SGC versus the tablet products are considered equivalent. It is also true that increasing patient exposures to lopinavir or ritonavir does not result in enhanced antiviral suppression—that is, no benefit to the patient is seen.

36. The Applicant is well aware that there is no additional therapeutic benefit to the
patient by using the tablet form over the SGC. To support its point, the Opponent refers to Exhibit C and the original data filed in Exhibit D, U.S Food and Drug Administration, Application Numbers 21-226 and 21-251, Clinical Pharmacology and Biopharmaceutics Review(s). Exhibit D contains reports that summarize the safety data, pharmacology of lopinavir levels versus varying dose combinations of lopinavir/ritonavir and the clinical outcomes (that is, viral load suppression) associated with these combinations.

37. In Exhibit C, the summary of outcomes of comparisons between the tablet versus SGC formulations (see page 8, section 2.2, and Table 2, page 4), affirm that no significant differences exist between the tablet and capsule formulations at steady-stage. This is confirmed by the statement on page 2, section 1.3 of Exhibit C (Exhibit page 57): "However, the results from a cross-study comparison indicate that the steady state pharmacokinetics of lopinavir and ritonavir... were similar to that seen in previous multiple dose studies in healthy subjects using SGC formulations." Exhibit C, page 2, section 1.3 also states "the new tablet formulation with slightly higher exposures compared to the capsule formulation is expected to have an efficacy profile similar to the capsule formulation."

38. In Exhibit D it is clear that the impact of higher levels of lopinavir exposure provided by the SGC were assessed before choosing the commercial dose for the original marketing submissions in the U.S. The Opponent refers to the following data presented in Exhibit D (Exhibit pages 154-155); Table 8.6.5.1.A "Week 24, 48 and 72, Proportion <400 copies /ml. and subsequent discussion, and Table 8.6.5.1.B "Week 24, 48 and 72 Proportion <50 copies /ml. and subsequent
discussion. These data clearly indicate the following:

- Lopinavir exposure following 400/200 mg BID... were >20% higher than that of 400/100 BID.

- These increased exposures did not, in fact, give better viral suppression. Instead, the 400/200 BID dose group of lopinavir/ritonavir (with the increased exposure to Lopinavir of >20%) in fact gave worse clinical results for viral suppression than the 400/100 mg BID dose group with the SGC. (See Exhibit C (Exhibit page 60)).

- There is firm cause to dismiss the Applicant’s claims to an enhanced efficacy with the new tablet formulation, because it is clear from their own prior data that enhanced exposure levels of LPV of >20% in fact lead to less effective viral suppression.

In conclusion, the relevant pharmacokinetic profiles and their relationship to patient benefit are presented by the Applicant in its submission for marketing approval (see Table 2, Exhibit C (Exhibit page 59) and Table in Exhibit D (Exhibit pages 123-124)). This table, in combination with Tables 8.6.5.1.A and 8.6.5.1.B on Exhibit pages 154-155 of Exhibit D demonstrate that even real, durable increases of “25%, 35% and 50% increase in Lopinavir Cmax, AUC and Cmin” do not result in enhanced efficacy, or suppression of the HIV virus in humans, for the patient. The Applicant asks us to conclude without data that very small increases in lopinavir Cmin will enhance the efficacy of Kaletra tablets. However, as shown by the Applicant’s own prior data, this is not the case.
Applicant has falsely argued that the legislative intent of Section 3(d) was to protect incremental innovation.

39. The Applicant is incorrect in stating on page 17, paragraph 4 of its statement that the legislative intent of Section 3(d) was to protect incremental innovation. The Opponent submits that the intent of Parliament in enacting Section 3(d) was to prevent the phenomenon known as evergreening by claiming inventions in trivial or incremental changes. This was to prevent the abuse of the patent system and to avoid an increase in prices to consumers, in particular in relation to the cost of medicines.

Amended claims 1-25 are not patentable under Sections 25(1)(e) and 2(1)j and 2(1)ja of the Act

40. The Opponent reiterates its arguments that the '339 does not amount to a technical advance and meet the requirement of inventive step under Sections 2(1)(j) and (ja). In its attempts to argue that '339 is not obvious to one skilled in the art, the Applicant has purposely adopted the rigid and narrow test that prior art or common general knowledge must 'teach' or 'suggest' the invention claimed in '339 in order to avoid the Opponent's evidence. This concept of obviousness has now been rejected by even the more liberal patenting regimes like the U.S. (see K.S.R International Co v Telesflex Inc 550 U.S. 358 (2007)) as not being the
correct approach. *KSR International Co v Teleflex Inc* has been accepted and relied upon by the Indian Courts. Indeed, if all prior art had to ‘teach’ a claimed invention for the purpose of being obvious, it would be more a case of novelty. The Opponent requests that the Honourable Controller adopt a more realistic and practical approach to the test of inventive step bearing in mind the common general knowledge that exists in the field relating to ‘339.

41. The Applicant relies heavily on the declaration of Jorg Breitenbach to support its case that the selection of substances to arrive at the formulation in ‘339 would not have been obvious to a person skilled in the art at formulating pharmaceuticals. The Opponent, while respectful of Mr Breitenbach’s resume, believes that his declaration cannot form the basis of an objective and honest assessment of one skilled in the art. This is because he is a co-inventor for ‘339 and is currently employed by the Applicant, Abbott Laboratories. Mr Breitenbach was also previously employed by BASF, Knoll AG/BASF Pharmaceuticals (BASF), from whom Abbott purchased the Meliex technology in 2001 - see attached Exhibit E, Soliq’s *All time History*. The Opponent will discuss the relevance of this point further below. Therefore, Mr Breitenbach, as an employee of the Applicant Abbott Laboratories, has a vested interest in seeing a patent granted for ‘339.

42. It is also worth noting from Mr Breitenbach’s resume, that he was awarded the ‘Abbott Life Cycle Management Award in 2005’, which coincides with the current application date and FDA approval of the claimed product in ‘339. As the Honourable Controller is probably aware, ‘life cycle management’ represents a strategy of companies to find opportunities of re-formulating existing compounds
to obtain additional patents that may not necessarily offer any new therapeutic benefits. As has already been demonstrated above, '339 offers no additional therapeutic benefits over the earlier formulation that is '677. The business practice of lifecycle management is largely used by pharmaceutical companies, like the Applicant, to maintain exclusivity over old compounds like ritonavir and lopinavir. This practice is more important today as companies like the Applicant are no longer investing R&D in new HIV compounds, but merely tweaking existing formulations with known techniques to prevent legitimate competition from entering the marketplace. In view of the above, the Opponent believes that Mr Breitenbach’s affidavit is inadmissible as it forms a biased opinion and not an objective assessment of what is obvious in the state of the art.

43. Before responding to the Applicant’s arguments regarding the obvious nature of selecting PVPs, surfactants and additives to formulate ‘339, the Opponent would like to elaborate on the context of the invention claimed in ‘339. In paragraph 31 of the Opponent’s statement, the Opponent has already argued that the Applicant has simply used an existing patented technology called Meltrex alongside commonly used formulation excipients, like PVP, for improving the solubility and bioavailability of ritonavir and lopinavir in solid dispersions. To that end the Opponent believes that the Applicant is attempting to confuse this patent office by suggesting that the use of common formulation excipients like PVP and surfactants deserves a patent.

44. To illustrate, Page 4 of Exhibit 12 of the Opponent’s statement, under the heading ‘Polymer/Drug Melt, describes the particular benefits of the Meltrex technology.
The Opponent also attaches Exhibit F, J. Breitenbach et al., *Two Concepts, One Technology: Controlled-Release Solid Dispersions Using Melt Extrusion (Meltrex)*, in Modified-Release Drug Delivery Technology, Volume I, Chapter 16, 2008 which provides a useful description of how Meltrex works. It should be noted here that although this publication is from 2008, the references clearly show this technology existed prior to the date of ’339. As Exhibit F shows, Meltrex technology provides a solvent free formation process and can be used to formulate crystalline drug substances into solid dispersions regardless of their particle size or polymorphic form. Meltrex enables the conversion of drugs to the amorphous state. An important part of the Meltrex process lies in the selection of appropriate polymer and excipients to provide solid dispersions. This is done through a screening system called Soliscreen®, which has been developed to *predict with a high level of confidence* the probability of being able to produce a stable solid dispersion of an active ingredient in a particular polymer matrix. It is also worth noting from the Applicant’s website, attached here as Exhibit G, Soliq’s *Meltrex Technology*, that Meltrex is promoted as technology that provides “opportunities for patent protection and life cycle management”.

45. Bearing in mind the above, the Opponent draws the Honourable Controller’s attention to statements made in Exhibit 7 of the Opponent’s statement and Annexure 6 of the Applicant’s statement. In Exhibit 7 and Annexure 6, the respective authors state that “incorporation of surfactants, acids or other wetting agents with traditional technologies (i.e. spray drying or older melt extrusion techniques) failed to provide adequate bioavailability for solid formulations. *Meltrex technology overcame these challenges.*"
46. It is clearly apparent therefore that the “inventive” aspect to ‘339 lies in the existing patented technology of Meltrex and not the selection of standard formulation excipients such as PVP, surfactants and additives. It is also clear that the Applicant’s claim of “years of intense research” went in to developing the current product actually relates to developing the Meltrex technology, for which BASF/Knoll (now owned by the Applicant, Abbott Laboratories) already has a patent, and not ‘339. Indeed, the fact that the Applicant only purchased Meltrex Technology in 2001 shows that the Applicant has not spent years of intense research on ‘339, but merely acquired an existing technology to create the formulation that is ‘339. As already demonstrated by the Opponent in its opposition statement, the use of PVPs and surfactants to formulate solid dispersions of compounds like ritonavir and lopinavir is general common knowledge. Indeed, on page 158, Annexure 7, of the Applicant’s statement, under the heading ‘Pharmaceutical Development’ the EMEA states in reference to the formulation that is ‘339 “all the excipients are commonly used for oral formulations...”

47. Without prejudice to the above, the Opponent will now respond to the Applicant with respect to its assertions that it would not have been obvious to use PVP with a surfactant to form an amorphous matrix.

The Applicant argues that none of the prior art and common general knowledge put forward by the Opponent in, Exhibit 8 (WO 01/34119 – ‘119), Exhibit 9 (US Patent No. 4,769,236 – ‘236), Exhibit 12 (BASF, ExAct Excipients and Actives...
for Pharma), Exhibit 13 (J Breitenbach, Melt Extrusion: from process to drug delivery technology), Exhibit 14 (A. Serajuddin, Solid Dispersion of Poorly Water Soluble Drugs), Exhibit 15 (O. Corrigan, Surfactants in Pharmaceutical Products and Systems), teaches or enables a person skilled in the formulations of solid dispersions to arrive at the current invention. As already stated above, the Applicant has deliberately adopted a narrow interpretation of the art and standard of obviousness to justify its patent. The Applicant claims that the Opponent uses "impermissible hindsight" to reconstruct the present invention. The Opponent disagrees with the Applicant's contention. If anything, the common general knowledge of using PVPs of a particular Tg value with surfactants to form an amorphous matrix within which to disperse the compounds like ritonavir and lopinavir provides the necessary foresight. For the Applicant to dress this issue in any other way is to effectively demote the skilled person in the art of formulation to a layperson in order to overcome obviousness.

48. On pages 23-35 of its statement, the Applicant contends that PVP is not used to form an amorphous matrix in '119. Instead, the Applicant contends that '119 uses PEG to form a crystalline matrix and the PVP functions as the crystallization inhibitor. The Opponent disputes this argument for the following reasons. '119 uses a PEG, which has an extremely low Tg (up to -55°C) to form a crystalline matrix. '339 on the other hand uses a PVP of Tg of 50°C or more to form an amorphous matrix. If as is claimed by the Applicant, the PEG in '119 has a very low Tg, then it cannot be crystalline. It will be amorphous at room temperature like PVP. Crystalline materials possess long-range order in the relative arrangement of molecules, and this long-range order is maintained while
molecular motion is inhibited. Above the Tg of a substance, molecular motion is seen and long-range order is substantially reduced or eliminated altogether. Therefore, the purpose of adding PVP to PEG is to ensure that the matrix in '119 does not crystallise, but remains amorphous. This being the case, '119 therefore uses PVP for the same purpose as is used in '339, to create an amorphous matrix. This is irrespective of the use of PEG. To claim inventiveness for removing PEG and increasing the amount of PVP with a surfactant, all which are described in '119, is disingenuous on the part of the Applicant. For the Applicant to contend that the PVP ratio in '119 does not form an amorphous matrix is simply a poor attempt by Applicant to distinguish '119 from '339 in order to overcome the inventive step requirement. Indeed, the overall intent of both '119 and '339 is clearly to maintain ritonavir, with or without lopinavir, in an amorphous form in the presence of whatever broad range of materials are needed to aid its dissolution. When this single end goal is met, and solubility is maintained, the overall objective of maximising bioavailability is achieved. This is clearly known as such by the article Devalina Law et al., Ritonavir-Peg 8000 Amorphous Solid Dispersions: In Vitro and In Vivo Evaluations, Journal of Pharmaceutical Sciences Vol. 93, No. 3, March 2004, attached as Exhibit H.

49. The Applicant also claims that the composition of '339 is unpredictable and inventive because it identifies that PVP should be used to form about 50% to about 85% (as per claim 1). This is not the case. A number of prior patents exist which disclose such a weight range for PVP in order to form an amorphous matrix within to disperse an active ingredient with very low solubility and low membrane permeability. For example, the earlier U.S. Patent No. 6,197,781 ('781), published
6 March 2001, attached as Exhibit I claims an oral pharmaceutical composition comprising rapamycin (a drug which has very low water solubility and membrane permeability) and related analogs in a solid dispersion in order to improve their solubility and bioavailability. '781 discloses the use of PVP to form a carrier medium (another term for a matrix). Column 2, line 31-33 states "the carrier medium is present in an amount of up to 99.99% by weight, for example 10-95 wt%." Therefore, this patent already discloses the range of PVP used in '239. Similarly U.S. Patent No. 4801460 in the name of BASF, published 31 January 1989, attached as Exhibit J discloses in column 4, lines 46-50 that the amount of NVP (which is another term for PVP) binder (a matrix former by another name) in the polymer matrix should not be less than 50%, preferably not less than 70% of all fusible binders. Indeed, '119 also infers on page 11, line 5 that "a range of 1-95% (w/w) of PVP can be employed."

50. The Applicant attempts to argue that the selection of polymers having a Tg of 50°C is also inventive. Once again the Applicant is ignoring general common knowledge. The Opponent relies on to two articles, A Forster et al. Selection of excipients for melt extrusion with two poorly water soluble drugs by solubility parameter calculation and thermal analysis, International Journal of Pharmaceutics, 226 (2001), 147-161, attached as Exhibit K, and A. Forster et al. Characterization of glass solution of poorly water soluble drugs produced by melt extrusion with hydrophilic amorphous polymers, Journal of Pharmacy and Pharmacology 2001, 53, 303-315, attached as Exhibit L. On page 148, left hand column, first paragraph of Exhibits K, the article explains that in order to form a glass solution that is physically stable over a long period of time, the glass
transition temperature should be higher than the storage temperature by at least 50°C. If room storage temperature is 25/30°C, then the Tg should be in the region of 80°C or more. Indeed this is the preferred Tg that ‘339 claims in claim 8 i.e. between 80-180°C. Table 4 in Exhibit L is also worth noting. As the various experiments show in Table 4, poorly water-soluble drugs with PVPs with a higher than 50°C Tg did not crystallise out. Based on the above literature, which would be commonly known by a skilled formulator in the field, the Applicant’s claims that selecting a PVP of between 80-180°C are not inventive. For the Applicant to suggest that no one skilled in the art would have thought to use a Tg value between 80-180°C for ritonavir or lopinavir, is to mislead this patent office.

51. The Applicant also attributes the improvement in ‘339 to the ‘unexpected’ success of using a surfactant within the amorphous polymer matrix. Again, the Opponent contests this assertion by the Applicant. Any skilled person in formulation, in particular in formulating solid dispersions, would know that for good product performance the use of a surfactant is preferred for a poorly water-soluble drug like ritonavir/lopinavir. Indeed, as shown the ‘781 patent, attached as Exhibit L, in column 3, line 24 states that the carrier medium (or matrix) may comprise one or more surfactants in an amount of up to 20% by weight. This is the same weight ratio of surfactant claimed by the Applicant in ‘339. The use of a surfactant with a PVP binder is also disclosed in Exhibit 12 on page 9. The authors of the paper refer to an earlier paper by Chen et al (1995) where they recommend the use of a surfactant like sodium lauryl sulfate in combination with Povidone in granulation to enhance the dissolution rate and therefore allow the preparation of harder tablets, which will still maintain good dissolution. For the
Applicant to suggest that selecting a surfactant with a HLB value of between 4-10 is inventive is to ignore the numerous textbooks on basic formulation techniques.

52. The Opponent refers to the basic textbook Howard C. Ansel et al., *Pharmaceutical Dosage Forms and Drug Delivery Systems*, Seventh Edition (1999), pages 367-369 attached as Exhibit M. Exhibit M is an example of just one basic textbook teaching that surfactants (also known as emulsifying agents or emulsifiers) are one of the fundamental types of formulation ingredients chosen to enhance rates of dispersion and water solubility for lipophilic substances like ritonavir and lopinavir. Surfactants exert their action by decreasing the surface tension that occurs between two layers, commonly between water and lipophilic or oily layers. It is also commonly taught that there are two types of emulsions: water-in-oil (w/o) and oil-in-water (o/w). Encouraging both of these types of emulsions in combination can commonly be important for pharmaceutical dosage forms. Surfactants with rather low HLB values (3-6) are known to encourage w/o emulsions. Surfactants with slightly higher HLB number (7-9) are classified as wetting agents. Wetting agents encourage the spread of water across the surface of lipophilic substances to yield enhanced dissolution properties. Surfactants with HLB 8-18 are classified as o/w emulsifiers, while those with values of 15-20 and above are commonly thought of as solubilisers and detergents. With such multiple uses, it is commonly known and taught in Pharmaceutical Sciences (often in a first-year PharmD course) that surfactants are used and that they are often used in combination. When one surfactant with rather low HLB value is called for, another surfactant of higher number may commonly be used to enhance the overall effect of emulsification, wetting and dissolution. The Opponent submits
that the Applicants claims do not differ conceptually from common teaching in this area.

53. In another attempt to further distinguish its claimed invention from the existing art, the Applicant insists that ritonavir is a Class IV compound according to the Biopharmaceutics Classification System (BCS). The Opponent disputes the Applicant's assertion. Attached as Exhibit N, is a search under the BCS, which lists ritonavir (and lopinavir) as Class II compounds. It is worth noting that the founder of the BCS system, Gordon L. Amidon, is also the president of the company TSRL from which these results were obtained. The classification of ritonavir as BCS class II is also found in other sources. For example on page 2 at [0016] of US. Patent No. 20060688010, attached as Exhibit O, ritonavir is described as BCS Class II. Therefore, solid dispersions of compounds like 17-Estradiol (BCS Class II) using 50% PVP and 40% Gelucire (a surfactant), as disclosed in Exhibit 13 of the Opponent's statement, would only serve to encourage formulators that there is a reasonable expectation that such combinations would work for other Class II compounds like ritonavir and lopinavir.

54. Even assuming arguendo that ritonavir is a BCS Class IV compound, between 1960 and 2002 more than 150 drugs in solid solutions and dispersions with PVP have been described in literature. Of these a number have been Class II and IV compounds. To illustrate, attached as Exhibit P, V. Buhler, Polyvinylpyrrolidone Excipients for Pharmaceuticals – Povidone, Crospovidone and Copovidone,
Springer (2005) is an extract from the referenced book explaining the benefits of PVP (povidone) and two tables (including the cited literature references), which show various prior publications discussing the improvement in bioavailability and stability of various active substances using solid solutions and dispersions in povidone. Examples of Class IV drugs from these tables include amoxicillin, furosemide, hydroflumethiazide, hydrochlorothiazide, nitrofurantion, phenobarbital and rifampicin. In light of the volumes of literature covering this area of formulations, it is disingenuous of the Applicant to claim that BCS Class IV compounds teach away from solid dispersions and solid solution formulations for other BCS Class compounds. To that end achieving the formulation in ‘339 would have been obvious to one skilled in this area.

55. In summary, the various exhibits provided by the Opponent go to show that there exists a significant amount of established common knowledge in the field of using PVPs to formulate compounds like ritonavir and lopinavir. This knowledge has been established over the span of nearly 50 years. It would not require a skilled formulator in the field to combine such literature as it has become standard knowledge in the field. For the Applicant to suggest that ‘339 offers an inventive step over this plethora of knowledge is to make the patent system redundant. It would mean every combination of commonly used excipients for a different compound would be patentable. Granting a patent for ‘339 would not only hurt the scientific community, it would also negatively affect the larger public interest.

The Application ‘339 does not meet the legal requirements under Section 8
56. Since filing its Opposition, the Opponent has learnt of an application that the Applicant is currently prosecuting in another country and that is the same or substantially the same invention as claimed in ‘339. The application in question is International Application No. PCT/US2006/005944 (International Publication No. WO 2006/091529), which has entered the national phase in India as Application No. 6733/DELNP/2007. Attached as Exhibit Q, is a copy of PCT/US2006/005944 (International Publication No. WO 2006/091529). This application covers a ‘Solid Pharmaceutical Dosage Formulation’ and is inordinately broad in its coverage so as to encompass the invention being claimed in ‘339. Indeed, this application has been designated European Patent Application No. 06735552.9 and has been objected to by the European Patent Office on the grounds of lack of novelty in light of the earlier corresponding European patent application to ‘339 (European Application No. 04816820.7). The Opponent attaches, as Exhibit R, a copy of the European Patent Office examination report for European Application No. 06735552.9.

57. The Opponent challenges that the Applicant has willfully failed to submit the detailed particulars of European Patent Application No. 06735552.9 and related patents around the world to this patent office as required under Section 8(1) of the Act. Aside from the fact that the later European Application No. 06735552.9 (6733/DELNP/2007) represents a clear example of double patenting, as well as an attempt to patent what is non-patentable subject matter, the Opponent request that the Honourable Controller should dismiss the present application under Section 8 for failure of the Applicant to submit detailed particulars on an application relating to the same or substantially the same invention.
The Opponent has clearly demonstrated in its opposition and response to the Applicant's statement and evidence that '339 does not meet the requirements of:

a) Section 3(d) - on the grounds that the subject matter claimed is a new form of a known substance that provides no enhancement of therapeutic efficacy over the existing form;

b) Sections 2(1)(j) and 2(1)(ja) - on the grounds that the invention would have been obvious to one skilled in the art in light of the substantial common general knowledge that exists in the particular field; and

c) Section 8(1) - on the ground that the Applicant has willfully not disclosed particulars of the same or substantially the same invention that is being prosecuted in another country.

The Opponent requests that the Honourable Controller rejects the Applicant's requests for costs as the opposition has been filed in good faith and there is no provision for such an award under the procedure of Section 25(1).

Dated this the 16th day of February 2009

For and behalf of the Initiative for Medicines, Access & Knowledge (I-MAK)

To:

The Controller of Patents

The Patent Office, MUMBAI