

# **The Patents Act, 1970**

**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 OPPONENTS”)**

**And**

**IN THE MATTER OF:**

**Indian Application No. 339/MUM/2006 filed on 23 August 2004 by Abbott Laboratories (“the APPLICANT)**

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## **STATEMENT OF CASE OF THE OPPONENT**

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1. The Opponent is a not-for-profit public service organisation having its registered address at 16192 Coastal Highway, Lewes, Delaware, 19958-9776, U.S.A. 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.
2. One such application of concern is Application No. 339/MUMNP/2006 A (‘339) titled ‘Solid Pharmaceutical Dosage Form’. ‘339 stems from International Application No. PCT/US2004/027401 filed on 23 August 2004,

claiming a priority date of 28 August 2003. '339 has now entered the national phase for India and this is confirmed by the fact that the application was published for opposition in Part II of the Official Journal of the Patent Office on 29 June 2007. A copy of the relevant publication for '339 is attached as **Exhibit 1**.

3. Rule 55(1)(A) of the Rules states that 'no patent shall be granted before the expiry of the period of six months from the date of publication'. In view of Rule 55(1)(A), it is understood that '339 has not been granted. Accordingly, as permitted under s25(1) of the Act and Rule 55(1), which allow *any person* to file a representation by way of opposition at the appropriate office (being the Mumbai Patent Office where '339 was filed) before the grant of a patent, the Opponent submits its opposition and supporting evidence to '339 on the grounds set out below. The Opponent, as is allowed under s25(1) of the Act and Rule 55(1) also requests a hearing in the matter.

### **Background to '339**

4. The HIV/AIDS epidemic poses one of the greatest challenges to global public health today, but even more so for developing countries, including India. Over 40 million people worldwide are infected with the HIV virus. The number of people infected with HIV/AIDS in India according to recent UNAIDS reports is 2.5 million, the second highest infected population in the world. Ritonavir and Lopinavir, which are known patented compounds and form part of the subject matter of '339 are HIV medications classified as

protease inhibitors. Ritonavir and Lopinavir have been highly prioritised for HIV treatment scale-up globally by organisations like the World Health Organisation, Clinton Foundation HIV/AIDS Initiative, Medecins Sans Frontieres, The Global Fund to Fight AIDS, Tuberculosis and Malaria and UNITAID. People Living With HIV/AIDS should be able to obtain access to the best and newest pharmaceutical treatments without undeserved patents making their availability too expensive or limited in supply.

5. '339 claims an invention for a new solid dosage formulation of the already disclosed Lopinavir/Ritonavir and its many other formulations that have been patented internationally. While '339 may be considered a new formulation of Lopinavir/Ritonavir, for the reasons set out in the grounds below, it is not an invention that should be considered patentable within the meaning of the Act. Should a patent be granted for the application in question, it will unfairly impede others from looking to develop and/or offer Lopinavir/Ritonavir at more affordable prices. Moreover, it will contribute to preventing HIV patients from accessing this particular treatment at a cost they can afford.

### **GROUND**

6. '339 claims an invention for developing a solid pharmaceutical dosage form comprising the HIV protease inhibitors Ritonavir and/or Lopinavir in at least one pharmaceutically acceptable water soluble polymer (with Tg of at least 50°C) and at least one pharmaceutically acceptable surfactant with HLB value from about 4 to about 10 (but preferably from about 7 to about 9). The

improvement that the Applicant claims through '339 is a solid dispersion of the poorly water-soluble compounds Ritonavir and/or Lopinavir, that yields high dissolution, suitable oral bioavailability and stability

7. As admitted by the Applicant on page 4, lines 16-28 of the specification, the compounds Ritonavir and Lopinavir, which are embodiments of the '339 application, have already been patented and disclosed in earlier applications. Ritonavir was disclosed in U.S Patent Nos. 5,542,206 (which we believe has been incorrectly numbered and should read 5541206), published on 30 July 1996, and 5,648,497, published on 15 July 1997. In addition, it should be noted that an application for a polymorph of Ritonavir has been filed for in India under PCT/2001/00018/MUM, which is currently pending. Lopinavir was disclosed in U.S Patent No. 5,914,332, published on 22 June 1999. The Applicant has also filed an application in India under IN/PCT/2002/1243 for a crystalline form of Lopinavir, also currently pending.
8. More specifically, the Applicant's claims within '339 may be summarised as follows:
  - a) Claim 1 relates to a solid pharmaceutical dosage form comprising at least one HIV protease inhibitor (including Lopinavir and/or Ritonavir), at least one pharmaceutically acceptable water-soluble polymer, with a Tg of at least 50°C and at least one pharmaceutically acceptable surfactant.

- b) Claims 2-8 are dependent on claim 1 and include a glassy solution or solid solution of a HIV protease inhibitor, a pharmaceutically acceptable surfactant with a HLB value from about 4 to about 10 alongside at least one further pharmaceutically acceptable surfactant being a sorbitan fatty acid ester and a solid dosage form comprising a particular weight of HIV protease inhibitor, a water-soluble polymer, a surfactant and additives.
  
- c) Claim 8 is dependent on Claim 1, but where the HIV protease inhibitor is Ritonavir.
  
- d) Claim 9 is dependent on Claim 8 and relates to claiming a dose adjusted Area Under the Curve (AUC) as tested in beagle dogs.
  
- e) Claim 10 is dependent on Claim 1, but where the HIV protease inhibitor is Lopinavir.
  
- f) Claim 11 is dependent on Claim 10 and relates to claiming a dose adjusted Area Under the Curve (AUC) as tested in beagle dogs.
  
- g) Claim 12 is dependent on Claim 1, but includes the combination of Ritonavir and Lopinavir.
  
- h) Claim 13 is dependent on Claim 12 and relates to claiming a dose adjusted Area Under the Curve (AUC) as tested in beagle dogs.

- i) Claims 14-17 are dependent on Claim 1, but cover a water-soluble polymer with a Tg of about 80 to 180°C, the water-soluble polymers homopolymer or co-polymer of N-Vinyl pyrrolidone, the co-polymer of N-vinyl pyrrolidone and vinyl acetate and at least one additive selected from regulators, disintegrants, bulking agents and lubricants.
- j) Claim 18 is dependent on Claim 1, but which contains a particular weight content of an HIV protease inhibitor at 40°C and about 75% humidity.
- k) Claims 19-21 are methods for preparing the solid dosage forms claimed in Claim 1 and its dependent claims, including preparing a homogenous melt and grinding the dispersion into a tablet for the purpose of preparing a medicament to treat HIV.
- l) Claims 22-23 relate to a solid dosage form comprising Ritonavir, a homopolymer of N-vinyl pyrrolidone, the surfactant sorbitan fatty acid ester and additionally at least one additive.
- m) Claims 24-25 relate to a solid dosage form comprising, a copolymer of N-vinyl pyrrolidone, the surfactant sorbitan fatty acid ester and additionally at least one additive.

- n) Claims 26-27 relate to a solid dosage form consisting of Ritonavir/Lopinavir, a copolymer of N-vinyl pyrrolidone and vinyl acetate, the surfactant sorbitan fatty acid ester and additionally at least one additive.
- o) Claims 28-30 relate to a solid dosage form comprising a particular amount of Ritonavir, a homopolymer of N-vinyl pyrrolidone, the surfactant sorbitan fatty acid ester and additionally at least one additive, wherein one additive is of a particular weight.
- p) Claims 31-33 relate to a solid dosage form comprising a particular amount of Lopinavir, a copolymer of N-vinyl pyrrolidone, the surfactant sorbitan fatty acid ester and additionally at least one additive, wherein additive is of a particular weight.
- q) Claims 34-36 relate to a solid dosage form comprising a particular amount of Ritonavir/Lopinavir, a copolymer of N-vinyl pyrrolidone, the surfactant sorbitan fatty acid ester and additionally at least one additive, wherein additive is of a particular weight.
- r) Claim 37 is a method for preparing the solid dosage forms claimed in Claims 22-26, including preparing a homogenous melt and grinding the dispersion into a tablet for the purpose of preparing a medicament to treat HIV.

9. The Opponent has closely studied the specification and claims made by the Applicant in '339 and strongly believe that Claims 1-37 are not patentable under the following grounds of s25(1) of the Act:

- a) s25(1)(f) – that the subject of any claim of the complete specification is not an invention within the meaning of this Act, or is not patentable under this Act, in particular under sections 3(d).
  
- b) s25(1)(e) – that the invention so far as claimed in any claim of the complete specification is obvious and clearly does not involve any inventive step having regard to the matter published as mentioned in clause (b) or having regard to what was used in India before the priority date of the applicant's claim.
  
- c) s25(1)(h) – that the applicant has failed to disclose to the Controller the information required by s8 or has furnished the information that in any material particular was false to his knowledge.

The Opponent submits its opposition on the following grounds:

**Claims 1-37 of '339 are not patentable under sections 25(1)(f) and 3(d) of the Act.**

10. The Opponent begins by placing emphasis on s3(d) and 25(1)(f). Section 3(d) states that 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”* does not amount to an invention and is not patentable under the Act. The ‘Explanation’ to Section 3(d) further sets out that *“salts, esters, ethers, polymorphs....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”*.

11. The Opponent stresses here that s3(d) is the logical starting point to assess whether '339 is an invention. Section 3(d) is situated within Chapter II of the Indian Patent(s) Act entitled ‘Inventions not Patentable – What are not inventions’. Therefore, s3(d) is to be read as an exclusion from patentability, which should be a threshold inquiry to assess whether the subject matter of an application qualifies as an invention. Under such an approach, only new forms of known substances conclusively demonstrating an enhancement of the known efficacy, should go on to be examined for novelty, inventive step or industrial application. This approach is clearly endorsed by the Draft Manual of Patent Practice and Procedure (2005), Indian Patent Office, page 65, submitted here as **Exhibit 2**. These draft guidelines are clear that patent

examiners should first consider whether an application meets the definition of what is an invention before proceeding to determine the patentability of the subject matter with respect to novelty, inventive step and industrial application. Therefore, the Opponent submits that the s3(d) analysis should be conducted first before moving on to the novelty or inventive step inquiries.

12. For purpose of s3(d), as already admitted by the Applicant on page 4, lines 16-28 of '339 and highlighted in paragraph 7 above, the compounds Ritonavir and Lopinavir, including its polymorphic forms, were already known. The Opponent further submits that the compounds Ritonavir and Lopinavir have also been disclosed in a pharmaceutical formulation through WO 00/74677 ('677), attached as **Exhibit 3**, published on 14 December 2000, otherwise known as the soft-gel capsule. It should be noted that '677 was also applied for in India and was allotted the application number IN/PCT/2001/01312/MUM ('01312). However, it is understood that the Applicant has withdrawn '01312. The Applicant has patented numerous versions of the Lopinavir/Ritonavir combination, including formulations. However, for purposes of narrowing the scope of the s3(d) efficacy inquiry, the Opponent focuses its attention on '677, which is known to provide the same efficacy, therapeutic effect and comparable bioavailability as the claimed invention '339. For purposes of clarity it should be noted here that this known soft-gel capsule was the version of Lopinavir/Ritonavir previously marketed to patients, a fact which bears relevance on the s3(d) efficacy analysis that is addressed in this representation of opposition.

13. As admitted by the Applicant, Ritonavir/Lopinavir and its various earlier disclosures noted in paragraph 7 above, were already recognised for their antiretroviral properties before the priority date of '339. Under s3(d), new forms of known substances, including combinations, are deemed to be the same substance. Section 3(d) does, however, contain the proviso that "*salts, esters, ethers, polymorphs....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***". The Opponent contends that claims 1-37 fail to meet the efficacy requirement as no relevant evidence is submitted to show that the claims differ significantly in properties with regard to efficacy. In the absence of a showing of enhancement of efficacy over the known combination Ritonavir/Lopinavir in '677 (**Exhibit 3**), the Opponent submits that '339 is merely the same substance as the previously known form and, therefore, should not even be considered a new form of known substance for the purpose of s3(d).

14. The Opponent further submits that there are various definitions of the term efficacy, all which require a therapeutic outcome. Pharmacological efficacy is defined as '*the strength of response induced by occupancy of a receptor by an agonist. It also describes the way in which agonists vary in the response they produce, even when they occupy the same number of receptors.*' Therapeutic efficacy refers to '*the ability of a drug to produce an effect, and refers to the maximum such effect.*' See **Exhibit 4**, *The Textbook of Pharmaceutical Medicine, Fourth edition 2002, Edited by John P Griffin and John O'Grady*). *Chapter 6 Clinical trials and good clinical practice by Nigel Baber and John*

*Sweatman*, page 283. Indeed, on pages 51-53 of the recent judgment in *Novartis AG v Union of India*, attached as **Exhibit 5**, the Chennai High Court referenced another definition, ‘*the ability of a drug to produce the desired therapeutic effect*’. From these basic definitions, it is evident that the term “efficacy” as adopted within s3(d) relates to the field of pharmaceuticals and the activity of the drug itself to produce an effect or response in the human body. As the Opponents will demonstrate, the Applicant has failed to show that the present application can meet such a standard.

15. The primary benefit claimed by ‘339 is the increased stability of the formulation. In light of the definitions set out above for efficacy, the Applicant’s claimed invention fails to meet the required standard and should be rejected. The formulation disclosed in ‘677 faced stability problems, which by Applicant’s own admission was solved by curtailing crystallisation in the soft-gel capsule, but also by alternatively developing ‘339, the melt-extruded tablet version of Ritonavir/Lopinavir. See page 1 of *Melt Extrusion Can Bring New Benefits to HIV Therapy, The Example of Kaletra® Tablets*, Breitenbach, American Journal of Drug Delivery, 2006, attached here as **Exhibit 6**. The primary benefit of the ‘339 tablet version is stability. However, stability is not the key factor that affects actual therapeutic outcome. Further, the other benefits, such as the ability to store at room temperature and lower pill burden/patient compliance do not satisfy the definitions of efficacy set out above, as efficacy is commonly referred to as either pharmacological or therapeutic, but ultimately must demonstrate a response or effect in the human body.

16. Having concluded that the Applicant's claim of stability does not amount to efficacy, as required under s3(d), the Opponent also establishes that the Applicant's claimed advantage of bioavailability is an attempt to mislead the Patent Office. The level of bioavailability of the '339 application is not unique to the application, as a similar bioavailability is present in the '677 patent. The Examiner should not be confused by Applicant's attempt to compare '339 to another melted formulation as shown in the Examples of the specification on pages 15-19. By the Applicant's own statements, it was only other *solid* forms of the known combination of Ritonavir/Lopinavir that exhibited poor bioavailability – but against the other well-known, widely prescribed form of the known combination Lopinavir/Ritonavir ('677), the Applicant did not and indeed could not claim significant difference in bioavailability or efficacy. See **Exhibit 6**, page 1, Abstract, paragraph 3. Indeed, in the same article by one of the Applicant's inventors, in a section entitled "*What does it mean for patients*", bioavailability and/or improved therapeutic effect is not even mentioned – because for patients, the actual bioavailability and/or efficacy of the drug is relatively insignificant. See **Exhibit 6**, page 3, section 2.3. Therefore the proper comparison warranting scrutiny from the Patent Office is assessment of the bioavailability of '339 against the *known* combination of Lopinavir/Ritonavir disclosed in Exhibit 3, the known soft-gel capsule combination, which the claimed invention '339 actually replaced on the market. Were such a comparison to be undertaken, the Opponent submits that the present application would demonstrate similarity in bioavailability and therapeutic effect to the known combination capsule patented under '677.
17. To further support the above contentions, the Opponent directs the Patent Office's attention to **Exhibit 7**, *New Tablet Formulation of Lopinavir/Ritonavir is Bioequivalent to the Capsule at a Dose of 800/200 mg*, Zhu et al, Abbott Laboratories, Poster presented at 45<sup>th</sup> Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), Washington DC, December 16-19, 2005. By the Applicant's own admission at the ICAAC Conference, a primary purpose to developing the tablet formulation was to 'maintain bioavailability similar to the SGC (soft-gel

capsule) formulation’. In its conclusion, the authors found that the tablet form exhibited only ‘slightly higher bioavailability’ than the soft-gel capsule. A marginal difference in bioavailability is certainly not a significant difference in efficacy and should be rejected under the s3(d) standard. The very title of Applicant’s poster drives this point home, as a strong statement of bioequivalence, and by that very definition, no significant difference in efficacy.

18. Taking all of the above facts under consideration, it is indisputable that claims 1-37 are insufficient to meet the standard under s3(d) and, therefore, should not be granted a patent.

**Claims 1-37 of ‘339 are not patentable under sections 25(1)(e) and 2(1)(j) of the Act**

19. In the alternative and without prejudice to the grounds raised above, claims 1-37 of ‘339 do not meet the requirements of the definition of an invention as provided in sections 2(1)(j) and 2(1)(ja) and are, therefore, objected to under s25(1)(e) of the Act.

20. Section 2(1)(j) states that an invention means a new product involving an inventive step. Section 2(1)(ja) qualifies the meaning of ‘inventive step’ as being a “feature of an invention that involves a *technical advance compared to existing knowledge* and that makes the invention *not obvious* to a person *skilled in the art*”. Section 25(1)(e) defines the abovementioned sections for the purpose of an opposition as “an invention which is obvious and clearly does not involve any inventive step having regard to matter published as

mentioned in s25(1)(b) or having regard to what was used in India before the priority date of the applicant's claim.”

21. Under the above definitions and the published matter/existing knowledge in the field prior to the priority date of ‘339 (28 August 2003), the Opponent is of the view that the subject matter of claims 1-37 do not amount to a technical advance and would have been obvious to a person skilled in the art.
  
22. The Opponent first draws this Patent Office's attention to the earlier published patent WO 01/34119 (‘119), attached as **Exhibit 8**, which discloses a solid dispersion comprising the HIV protease inhibitors Ritonavir and/or Lopinavir in a water-soluble carrier Polyethylene Glycol (PEG), a crystallisation inhibitor Polyvinylpyrrolidone (PVP) and surfactants in order to inhibit crystallisation, improve the aqueous dissolution properties and improve bioavailability of active ingredients (including Ritonavir and/or Lopinavir). In particular, Examples 1 and 2 on pages 19 and 20 and claims 1-10 of ‘119 disclose a solid dispersion comprising the water-soluble polymers PEG and PVP, surfactants and antioxidants. In light of ‘119, it would have been obvious for the Applicant to select water-soluble polymers like homopolymers and copolymers i.e. PVP, as set out on page 8 and of ‘339, alongside surfactants in order to make poorly water-soluble compounds like Ritonavir and/or Lopinavir have better dissolution with suitable oral bioavailability and stability.

23. The Applicant is likely to attempt to distinguish the technical features of ‘119 from the present application by arguing that ‘339 uses an amorphous matrix formed by PVP or other polymers having a Tg of at least about 50°C, as opposed to a crystalline matrix formed by PEG or similar carriers. The Applicant is also likely to argue that ‘119 does not suggest that the PEG matrix (or like crystalline matrix) can be eliminated without affecting the bioavailability of the dispersed drugs and, therefore, does not specifically teach or suggest to a skilled person that Ritonavir/Lopinavir can be directly dispersed in a matrix formed by PVP or that PVP could be directly used to form its own matrix where drugs can stably be dispersed.

24. While ‘119 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, ‘119 does disclose prior art that clearly suggests this.

25. On page 5, line 15 of ‘339, reference is made to the earlier US Patent 4,769,236 (‘236), attached as **Exhibit 9**, which discloses a process for the preparation of a stable pharmaceutical composition with high dissolution rate in the gastrointestinal tract containing PVP. In particular, Column 1, Lines 54-65 of ‘236 clearly indicates the use of PVP alone to lend stability and solubility by holding the medicament in the amorphous form. Therefore, it would have been obvious from the ‘236 patent that poorly water-soluble compounds like Ritonavir/Lopinavir can yield a high dissolution rate in the

gastrointestinal tract and stability when using PVP alone as a matrix. As any ordinary person skilled in the art would admit, yielding a high dissolution rate in the gastrointestinal tract would be the primary objective for a poorly soluble drug like Ritonavir/Lopinavir.

26. The Opponent would like to draw the Patent Office's attention to a letter of 1 March 2004 addressed by the Applicant to the European Patent Office when prosecuting '119, attached as **Exhibit 10**. In its letter, the Applicant argued that the '236 patent, which formed the D2 prior art in the examination report and International Search Report, attached as **Exhibit 11**, was speculative with regard to the use of PVP in a water soluble matrix in that no examples using such a matrix are disclosed. The Applicant also argued in the prosecution of its application '119 that '236 was speculative with regard to the pharmaceutical compounds that can be stabilised by PVP, the only examples given in '236 being hydroflumethiazide-PVP and dipyridamole-PVP mixtures and not Ritonavir or Lopinavir.

27. In anticipation that the Applicant will raise the same arguments for its '339 application, in that '236 does not specifically suggest a PVP water-soluble matrix for Ritonavir/Lopinavir, the Opponent contends that such an argument should be rejected. It would have been well known to one ordinarily skilled in the art that the compounds hydroflumethiazide and dipyridamole are well recognised for being good examples of poorly water-soluble compounds like Ritonavir/Lopinavir. As '236 suggests the use of a PVP matrix for hydroflumethiazide and dipyridamole, it would have been obvious to try

PVP, with more than a reasonable expectation of success, for other poorly soluble compounds like Ritonavir/Lopinavir. Further proof of this fact is shown by the common general knowledge references set out below.

28. That PVP could be used to form its own matrix is made all the more obvious by ‘119 on page 10, lines 15-24 through to Page 11, Lines 1-5 and Figures 5-8, which identify the utility of PVP in providing a stable, non-crystalline (amorphous) matrix for drug delivery. Given the existing knowledge available to one skilled in the art, discussed in more detail below, and 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. Moreover, as is known from the existing knowledge in the art, using PVP would have been the obvious choice of a water-soluble polymer for use with the melt extrusion process.

29. In order to further support the above points, there exist numerous prior literatures that irrefutably show it was existing common knowledge to directly utilise PVPs to form its own amorphous matrix, where drugs with poor water solubility, like Ritonavir/Lopinavir, can stably be dispersed as claimed in ‘339. It would also have been known that using a PVP matrix would not be detrimental to the bioavailability of poorly soluble compounds. In fact, as the following literature shows, it was common knowledge before the filing of ‘339 that a PVP matrix would improve the bioavailability of

poorly soluble compounds. The following literatures are only a few examples selected from numerous prior articles, but which the Opponent believes make the point clear to one skilled in the art.

30. Attached as **Exhibit 12** is a supplement from the company BASF, *ExAct – Excipients and Actives for Pharma*, No. 2, July 1999 (BASF). It should be noted that this supplement is from the company that the Applicant acquired its Meltrex technology from in 2001 for the purpose of hot melt extrusion. This extrusion process is used to make the solid dispersion claimed in ‘339 as mentioned on page 10, lines 8-19. **Exhibit 12** includes various short articles on PVPs by different authors. In the article by H. Witteler et al, *Great 60 Years of Polvinylpyrrolidone – Chemistry and Physiochemical Properties of Povidone* (Witteler), on page 3 under the heading ‘Complex Formation with soluble PVP’ the authors state:

*“Due to their chemical structure, namely the amide bond, PVP forms a variety of complexes with other chemical compounds including pharmacological actives. For these compounds, complexation results in either **enhanced solubility, improved bioavailability or increased stability.**”*

31. On page 4 of **Exhibit 12**, under the heading ‘Polymer/Drug Melt Extrusion’, Witteler et al. go on to state: *“As a result of close collaboration over the past ten years, Knoll AG and its parent company BASF have developed a patent-protected novel pharmaceutical manufacturing technology: drug is incorporated by melt extrusion in a matrix consisting of a pharmaceutical*

*polymer. Due to its thermoplasticity and balanced aqueous solubility properties, Kolidon(PVP) grades have been found to provide a comprehensive and universal base for various types of drugs. After melt extrusion, the active drug can present in the extrudate in one or two forms: as a crystal suspended in the hardened Kollidon matrix, or as a molecule dissolved in the polymer during the melting phase and remaining dissolved in the finished product – a “solid solution”. Melt extrusion paves the way for benefits in therapy.”* The bullet points following the above paragraph then set out the benefits of polymer/drug melt extrusion, namely: formulation with **controlled release** (instant and sustained release) and **improved bioavailability for compounds with low aqueous solubility** (as Ritonavir/Lopinavir are known to be). As mentioned above, it should be noted that the Applicant acquired the Meltrex patented technology referred to by Witteler et al. in 2001 in order to control the problem of crystallisation, while obtaining bioavailability in solid forms of Ritonavir/Lopinavir. Based on the above disclosure, it is clear that the use of a 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.

32. In order to provide further perspective to the existing knowledge set out in **Exhibit 12** above, the Opponent attaches the article by Jorg Breitenbach, *Melt Extrusion: from process to drug delivery technology*, European Journal of Pharmaceutics and Biopharmaceutics, 54, 2002, 107-117 (Breitenbach), attached as **Exhibit 13**. **Exhibit 13** reviewed suitable water-soluble polymers and excipients that had already been successfully adopted for poorly water-

soluble drugs. See for example, page 114, first paragraph, left hand column, the author provides an example where the poorly water-soluble drug 17-Estradiol hemihydrate showed a 30-fold increase in dissolution for a formulation containing 10% 17 Estradiol, 50% PVP and 40% Gelucire 44/14. As already set out in **Exhibit 12** above, the use of melt extrusion technology had made it easier to apply already known water soluble polymers, like PVP and hydroxypropyl cellulose, in order to aid solid dispersion. To that end, it has to be recognised 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.

33. Further evidence showing that using water-soluble polymers like PVP could be used as a carrier for solid dispersions can be found in Abu. T. M. Serajuddin, *Solid Dispersion of Poorly Water-Soluble Drugs: Early Promises, Subsequent Problems, and Recent Breakthroughs*, Journal of Pharmaceutical Sciences, Vol 88, No. 10, October 1999 (Published on Web 27/8/1999) (Serajuddin), attached as **Exhibit 14**. Serajuddin states on page 1061, right hand column at the beginning of the last paragraph:

*“The conversion of drug to crystalline state is also the primary stability issue with solid dispersions prepared by the solvent method. **PVP**, which is commonly used as a carrier in such solid dispersions, is amorphous and does not convert to a crystalline state. However, certain other carriers may convert from their amorphous states to crystalline states in solid dispersions..... Doherty and York studied the stability of furosemide-PVP*

*solid dispersion in the temperature range of 6 to 45 °C and 40% RH for up to 1 year. They did not observe any crystallization of furosemide and suggested that **PVP may indeed act as a stabilizer in the solid dispersion by retarding crystallization of drug at a relatively low humidity.***”

34. With respect to the argument that it would not have been obvious to use a PVP to form an amorphous matrix which would provide suitable bioavailability for a poorly-water soluble drug like Ritonavir and/or Lopinavir, the Opponent refers to Owen Corrigan et al, *Surfactants in Pharmaceutical Products and Systems*, Encyclopedia of Pharmaceutical Technology, Vol 14, 2002, at page 2649 (Corrigan), attached as **Exhibit 15**. Under the heading ‘Solid Dispersion Systems’ Corrigan et al. clearly state:

*“The **bioavailability of hydrophobic drugs can be increased** by strategies designed to enhance the dissolution rate of the drug. This has been 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.**”*

35. In anticipation of the Applicant raising the argument that it would not have been obvious to have selected surfactants with HLB values between 4-10 (preferably from about 7-9), it should be recognised that one ordinarily skilled in the art would know to use surfactants within this range of HLB in order to improve the solubility of a hydrophobic drug like Ritonavir/Lopinavir. Reference books, such as the *Handbook of Pharmaceutical Excipients*, Raymond Rowe et al, APhA Publications, 4<sup>th</sup>

Edition, 29 May 2003, lists many of the surfactants adopted in '820 and provides clear examples of their particular uses and benefits. For example, polyoxyethylene alkyl esters are widely used for oral pharmaceutical formulations to enhance the aqueous solubility and dissolution of poorly soluble compounds such as Ritonavir/Lopinavir. They are known to be stable, hydrophilic, water-soluble and offer physical stability for storage purposes. Indeed the Applicant has already disclosed the surfactant polyoxyl 35 castor oil, sorbitan fatty acid esters, like sorbitan mono laurate, and many of the other surfactants listed in '339 for formulating Ritonavir/Lopinavir in the soft-gel capsule (see pages 24 and 25 of the attached '677, **Exhibit 3**).

36. The above points also stand with respect to the obvious nature of selecting a water-soluble polymer with a suitable Tg to be used with the Meltrex technology. Indeed all the literature provided above suggest this.
  
37. In light of '119, '236 and the knowledge and technology that existed prior to the filing of '339 as shown above, it is difficult to see how the Applicant can claim that using a water-soluble polymer like PVP, with known substances like surfactants and additives that are commonly used for formulation purposes, amount to a technical advance that would not have been obvious to one skilled in the art. In view of the above, '339 does not have any inventive step. The techniques used in '339 would have been obvious to try with more than a reasonable expectation of success expected by one ordinarily skilled in the art.

**Claims 1-37 of the invention are not patentable under the sections 25(1)(h) and 8 of the Act.**

38. Following the passage of the Patents (Amendments) Act 2005, Section 8(1)(a) and (b) now makes it an obligation on the applicant to keep the Controller informed, up to the date of grant of the patent application in India, of the same or substantially similar application which is being prosecuted in another country. This obligation requires the Applicant to provide, within a prescribed period as the Controller may allow, a statement setting out detailed particulars of the application being prosecuted in another country. Section 8 is read into s25(1)(h) as ground of opposition to the grant of a patent. Based on the above, the Opponent questions whether the Applicant has provided the information and particulars of the equivalent foreign applications that the Applicant is currently prosecuting to this Patent Office.

39. In particular, the Opponents are aware that the Applicant has applied to patent the same invention claimed in '339 at the European Patent Office Application No. 04816820.7. The Opponent understands that European Patent Application No. 04816820, which is currently under examination, has been objected to on the grounds that it does not meet the requirements of patentability required under the European Patent Convention. In the event that the Applicant has failed to meet its obligations under s8, the application should be rejected in its entirety.

Based on the grounds set out in paragraphs above, the Opponent requests that Application No. 339/MUMNP/2006 A be refused in its entirety. As permitted under Section 25(1) of the Act and Rule 55(1) of the Rules, the Opponent requests that this Patent Office informs the Opponent immediately of any response filed by the Applicant to this opposition and also grant the Opponent a hearing in the above matter.

Dated 16 day of August 2007

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

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

To:

The Controller of Patents

The Patent Office, MUMBAI