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Our Ref: I-MAK/Abbott - 04816820.7
Your Ref: 3820 MNMms

Attention: Sophie Muller (Primary Examiner – Examining Division)
European Patent Office
D-80298 Munchen
Germany

13 August 2007

Dear Ms Muller

Third Party Observation under Article 115 of the EPC against European Patent Application No. 04816820.7 -1219 in the name of Abbott Laboratories

The Initiative for Medicines, Access & Knowledge (I-MAK) is a not-for-profit public service organisation consisting of lawyers and scientists working to protect the public domain against undeserved patents. I-MAK works to ensure that patents do not act as a barrier to research and restrict the public's access to affordable medicines.

One such patent application of concern is European Patent Application No. 04816820.7 ('820). Accordingly, under Article 115 of the European Patent Convention (EPC) we set out below our observations and the grounds under the EPC as to why '820 does not merit a patent.

Background to '820

The HIV/AIDS epidemic poses one of the greatest challenges to global public health today. Roughly over 40 million people worldwide are living with HIV/AIDS, with approximately 1 million in Western and Eastern Europe.¹ People Living with HIV/AIDS should be able obtain access to the best and newest pharmaceutical treatments available without undeserved patents making their availability too expensive or limited in supply.

¹ See http://www.unaids.org/en/HIV_data/epi2006/default.asp. The figure of 1 million is an estimate given that figures for Eastern Europe are calculated to include Central Asia.

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Lopinavir and Ritonavir are HIV medications classified as protease inhibitors. The Lopinavir/Ritonavir combination is recommended by the World Health Organisation and is considered to be the backbone of treatment scale-up globally. Indeed, entities including European/international organisations Medecins Sans Frontieres, The Global Fund to Fight AIDS, Tuberculosis and Malaria and UNITAID have highly prioritised the Lopinavir/Ritonavir combination to save the lives of patients across the world.

The Applicant in '820 makes the claim that it has developed a new solid dosage formulation of the already disclosed Lopinavir and/or Ritonavir compounds and its many other patented formulations. Should a patent be granted for the application in question, it will unfairly impede others from offering, and HIV patients receiving, Lopinavir/Ritonavir at more affordable prices.

Although the above issues are not the grounds for our observation under Article 115, we respectfully ask that they be taken into full consideration when examining '820.

Grounds of Observation – Article 56 EPC

The grounds of this observation, as set out in detail below, are based on Article 56 of the EPC and are directed at all the amended claims, 1-32, as filed by the Applicant in its letter of 20 July 2007.

Article 56 provides that an invention shall be considered as involving an inventive step, if having regard to the state of the art, it is not obvious to a person skilled in the art. Article 54(2) defines the state of the art to comprise everything made available to the public by means of written or oral description, by use, or in any other way, before the date of filing of the European patent application.

'820 stems from International Application No. PCT/US2004/027401 filed on **23 August 2004**, claiming a priority date of **28 August 2003** from US application no. 650178. The Applicant claims the invention in '820 adds to the existing art by 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 examination report of the European Patent Office (EPO), dated 10 January 2007, has identified WO 2004/032903 (D1) and WO 01/34119A3 (D2) as the two closest prior art. The EPO believes the above prior art already discloses the invention in '820 and, therefore, makes it devoid of any novelty or inventive step. The Applicant, in its response of 20 July 2007, argues that '820 can be distinguished from D1 and D2. In particular, the Applicant contends:

1) D1 uses cross-linked nonthermoplastic carriers as the backbone of its matrix, within which the active ingredients are dispersed. One ordinarily skilled in the art would not understand a cross-linked nonthermoplastic to be water-soluble unless the crosslinks break by water, which is not intended by D1. Also, a cross-linked thermoplastic carrier is not capable of having a Tg of about 50°C. In contrast, '820

uses a water-soluble polymer as the matrix of its back bone, where the water-soluble polymer has a Tg of at least 50°C. Therefore, D1 does not teach or suggest the use of water-soluble polymers as the backbone of the matrix.

2) '820 can be distinguished from D2 by two features. The first is that '820 uses an amorphous matrix formed by PVP or other polymers having a Tg of about 50°C, as opposed to a crystalline matrix formed by PEG or similar carriers. Second, D2 does not suggest that the PEG matrix (or like crystalline matrix) can be eliminated without affecting the bioavailability of the dispersed drugs. Therefore, D2 does not specifically teach or suggest 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.

D2, US 4,769,236 and common general knowledge make the choice of stably dispersing Ritonavir/Lopinavir in a PVP matrix without impairing bioavailability obvious to the ordinary skilled person in the art.

D2 and US 4,769,236:

The arguments raised by the Applicant with respect to D2 as set out above in point 2 are not only misleading, but also fail to take into account the common general knowledge that exists in the state of the art.

On page 5, line 15 of D2, reference is made to the earlier US Patent 4,769,236 ('236), a copy of which is attached, which clearly teaches 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 a poorly soluble drug (which Ritonavir/Lopinavir are known to be) 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.

We note from the Applicant's response of 1 March 2004 to the EPO when prosecuting D2, a copy of which is attached, it argued that the '236 patent (which formed the D2 prior art in the examination report) 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 D2 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 (ABT-378).

It is likely that the Applicant will raise the same arguments for its '820 application in that '236 does not specifically suggest a PVP water-soluble matrix for Ritonavir/Lopinavir. However, 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 soluble compounds like Ritonavir/Lopinavir. As '236 suggests the use of a PVP matrix for hydroflumethiazide

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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.

That PVP could be used to form its own matrix is made all the more obvious by D2 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 common general knowledge available and as could be inferred from D2, an ordinary skilled person 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 common general knowledge, using PVP would have been the obvious choice of a water-soluble polymer for use with the melt extrusion process.

Common General Knowledge

D2 and '236 are not the only prior disclosures that suggest the use of PVP to form an amorphous matrix within which to disperse a poorly water-soluble drug like Ritonavir/Lopinavir. There exist numerous prior literatures that irrefutably show it was common general knowledge to directly utilise PVPs to form its own amorphous matrix, where drugs with poor water solubility (like Ritonavir/Lopinavir) can stably be dispersed. 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 '820 that a PVP matrix would improve the bioavailability of poorly soluble compounds.

The following literature are just a few examples selected from numerous prior articles that confirm the points set out above:

A) BASF, *ExAct – Excipients and Actives for Pharma*, No. 2, July 1999 (BASF). This supplement, from the company that Abbott acquired its Meltrex technology from in 2001 for the purpose of hot melt extrusion, includes various pieces on PVPs by different authors. In the article by H. Witteler et al, *Great 60 Years of Polvinylpyrrolidone – Chemistry and Physicochemical 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**.”

On page 4, under the heading 'Polymer/Drug Melt Extrusion', Witteler et al. 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 in manufacturing of Ritonavir/Lopinavir.² Based on the above disclosure, it is clear that the use of a PVP to form its own amorphous matrix as claimed in ‘820 did not involve any inventive step and was merely the use of known knowledge and technology.

B) Jorg Breitenbach, *Melt Extrusion: from process to drug delivery technology*, European Journal of Pharmaceutics and Biopharmaceutics, 54, 2002, 107-117 (Breitenbach).

In order to provide further perspective to the common general knowledge set out in (A) above, the article by Breitenbach suggested the course of future developments for solid dispersions and melt extrusion technology. The article reviewed suitable water-soluble polymers and excipients that had already been successfully adopted. 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 (A) 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 required no inventive step, but was simply made predictable given known technologies at that time such as melt extrusion.

C) 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).

In the above article, on page 1061, right hand column at the beginning of the last paragraph, Serajuddin states:

² See the attached article by Jorg Breitenbach, *Melt Extrusion Can Bring New Benefits to HIV Therapy – The Example of Kaletra® Tablets*, American Journal of Drug Delivery, 4(2): 61:64, 2006. The article states on page 61, in the final two paragraphs of the introduction, that because the active ingredients Ritonavir and Lopinavir could crystallize out of solution reducing bioavailability, the existing product was reformulated using melt extrusion, which ‘820 relates to.

“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.”

D) Owen Corrigan et al, *Surfactants in Pharmaceutical Products and Systems*, Encyclopedia of Pharmaceutical Technology, Vol 14, 2002, at page 2649 (Corrigan), under the heading ‘Solid Dispersion Systems’ 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.**”

D1

With respect to the arguments raised by the Applicant in its letter of 20 July 2007, we would like to make the following observations:

- a) D1 specifically teaches that a cross-linked PVP can be used as a swellable, non-soluble, backbone of a matrix.
- b) D1 also teaches the use of an adjuvant polymer that is water-soluble in order to enhance the dissolution of the active ingredient, page 3, lines 20-31 of DE 102 47 037 as attached to the Applicant’s response of 20 July 2007.
- c) The Applicant’s assertion that a cross-linked nonthermoplastic carrier cannot have a Tg of at least 50°C is incorrect. As anyone ordinarily versed in the art would be able to identify, there are several cross-linked nonthermoplastic carriers that have a Tg of at least 50°C.

Taking the above into account, D1 would have suggested to one ordinarily skilled in the art to use a water-soluble polymer like PVP to form the backbone of a matrix for enhancing drug dissolution and solubilising a compound like Ritonavir/Lopinavir. This is particularly so in light of the existing literature identified above.

Use of surfactants and water-soluble polymers with particular HLB values and Tg.

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, 4th 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 that need 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 mono laurate and many of the other surfactants listed in '820 for formulating Ritonavir/Lopinavir in a soft-gel capsule (see pages 24 and 25 of the attached WO 2000/74677).

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 the literature provided above suggested this.

Conclusion

Based on the above observations, '820 involves no inventive step in light of the suggested teachings of D1, D2, '236 and common general knowledge. The techniques used in '820 would have been obvious to try with more than a reasonable expectation of success expected by one ordinarily skilled in the art. It is our respectful observation that the EPO should reject this application in its entirety.

We should be grateful if you could acknowledge safe receipt of this letter and confirm that it will be communicated to the Applicant.

We look forward to hearing from you.

Yours sincerely

Tahir Amin/Priti Radhakrishnan

Initiative for Medicines, Access & Knowledge (I-MAK)