

Summary of Pre-grant Observation/Opposition in Europe and India against Abbott Laboratories Application for the ‘Heat Stable’ Lopinavir/Ritonavir Tablet Formulation

On 16 August 2007, the Initiative for Medicines, Access & Knowledge (I-MAK), announced its filings of a pre-grant observation at the European Patent Office (EPO) and a pre-grant representation of opposition at the Mumbai Patent Office, against Abbott’s patent application for its ‘heat-stable’ tablet formulation of Lopinavir/Ritonavir.

Background to Abbott’s claimed invention

As known to many in the health field, the tablet which combines Ritonavir and Lopinavir, otherwise known as Aluvia® or ‘heat-stable Kaletra®’, does not require refrigeration. The tablet also reduces the number of pills that a patient needs to take when compared to the previously marketed soft-gel capsule. These developments have been heralded as important, but do they merit an invention and an exclusivity period of 20 years?

Abbott’s application claims an invention for a solid oral dosage formulation (the heat stable tablet) for protease inhibitors, in particular Ritonavir and/or Lopinavir, which will increase their solubility in water, provide suitable bioavailability and stability – the effects of which include lower pill burden and non-refrigeration. By combining known water-soluble polymers, surfactants, excipients with a known hot melt extrusion technology acquired by Abbott from BASF in 2001 (Meltrex® Technology), Abbott claims they have invented a new tablet that would not have been known or obvious to one skilled in the field.

The Grounds

Under Art 115 of the European Patent Convention and s25(1) of the Indian Patents Act *any person* is entitled file an observation/opposition prior to the to the grant of a patent application based on a number of grounds available. These include, but are not limited to:

- that the claimed invention had already been published;
- that the invention claimed does not involve any inventive step and would have been obvious to a person working in the relevant field.

In India, there exists an additional ground (section 3(d)), which requires the applicant to show that in order to be considered an invention, an application for a new form of a known substance, in this case Ritonavir/Lopinavir, must show an *enhancement of efficacy* over what was already known. Failure to show such an enhancement means that the alleged new form is still considered to be the same substance and, therefore, not an invention.

The Arguments

Taking these grounds, strong arguments, backed by credible publications and evidence, have been submitted. The observation/opposition raise serious questions about why Abbott's claim for a new solid dosage formulation for Ritonavir/Lopinavir does not amount to an invention. The main grounds of the pre-grant observation/opposition rest on the following points:

1. One of Abbott's main claims is that this tablet is new and not obvious to select a water-soluble polymer i.e. Polyvinylpyrrolidone (PVP), with a glass transition temperature of about 50°C to form an amorphous matrix, in order to improve dispersion of poorly water-soluble compounds like Ritonavir/Lopinavir.

However, there exist earlier patents and numerous literatures that show that it was obvious to do what Abbot is claiming. An earlier formulation patent by Abbott (WO 01/34119) and US Patent No. 4,769,236 *already adopt water-soluble polymers like PVP* in order to achieve the claims made in the latest application. This fact is compounded by a large number of earlier scientific publications in the field.

One particularly revealing marketing publication is from BASF in 1999 (*from whom Abbott purchased the known Meltrex® technology in 2001 for the very purpose of formulating solid dosage forms*), which explains that PVPs can be used with Meltrex® to form solid dispersions of poorly water-soluble drugs, like protease inhibitors, that achieve stability and bioavailability. Other earlier literatures in the field confirm this, which raises serious doubts over Abbott's claim that this tablet is an invention.

2. Abbott's claim to use particular surfactants with a particular range of hydrophilic-lipophilic balance is also obvious in the light of earlier patents and literatures. Indeed, what Abbott has done is *to use the same surfactants that it adopted in its earlier patent application for what is known as the soft-gel capsule version of Kaletra®*. Moreover, to a person working in the field of tablet formulation, the properties of surfactants and how they work on poorly water-soluble drugs, like

Ritonavir/Lopinavir, is well known from basic textbooks such as the Handbook of Pharmaceutical Excipients.

3. With respect to India, the additional argument of efficacy (section 3d) was raised. While the definition of what amounts to efficacy of a known substance is still to be decided following the Glivec® case, it seems that India is likely to lean toward an interpretation that relates to an enhancement that is therapeutic. Interestingly, as Abbott has admitted itself at a conference in 2005 (see Zhu et al. *New Tablet Formulation of Lopinavir/Ritonavir is Bioequivalent to the Capsule at a dose of 800/200mg*) the new tablet form is bioequivalent to the earlier soft-gel capsule – effectively meaning there is no significant difference in bioavailability. Abbott may claim improved stability meets the efficacy test, but that seems an unlikely interpretation.

For more information see: www.i.mak.org/lopinavirritonavir/