

# Polymorphism and Patentability: Shaping India's Legal Standards



# Intersection of science and law

- Polymorphs are a strong case study of the pharmaceutical industry, drug development and the complex interplay of law and science.
- *Gleevec* decision highlights some of these issues, particularly for efficacy test under s3d.

# Science of Polymorphs

- Solid forms of compounds exist in more than one crystalline form.
- This phenomenon, known as polymorphism, manifests as molecules arrange themselves differently in crystal lattice.
- Polymorphs can be crystalline, amorphous, solvate or hydrate.

# Science of Polymorphs, Cont.

- Different polymorphs may have different properties, including solubility, stability and bioavailability.
- These properties are believed to impact manufacturing process and the safety or effectiveness of the drug.
- “Seeding Phenomenon”- When a crystal form of a new compound is developed, it becomes much easier to crystallise more forms of the compound, since crystals may be airborne and therefore ‘present’.

# Law Impacting Polymorphism

- Traditional issues: Novelty, Inventive Step, Industrial Application
  - Is new polymorph new in light of prior art?
  - Does the new polymorph meet inventiveness standard, depending on countries laws? Does it show a technical advance, a pharmacological advantage?
  - What use will the polymorph have? How useful must it be?

# India and Polymorphs

2005 draft Manual for Examiners:

“Some therapeutically active ingredients present polymorphic forms, that is, they may crystallize in diverse forms, which may have different properties that are more or less significant in terms of their therapeutic use. Such forms can be deemed within the prior art – **and therefore non-patentable** – if they were inevitably obtained following the process of the basic patent on the active ingredient or were covered by a previous product patent.”

- The Manual fails to assess the different properties of polymorphs regarding therapeutic use.
- Additionally, hydrates are unpatentable on the basis of inventive step.

# Case Study: Ritonavir

- Ritonavir, or Norvir<sup>®</sup>, was patented in 1993 and marketed in 1996 by Abbott Laboratories.
- The drug was on the market for 18 months before a serious problem emerged: the drug began precipitating out of formulation in large quantities.

# Case Study: Ritonavir

- The new form was dubbed Form 2, and was found to be less soluble. This led to a disadvantage for patients who needed to get higher quantities of the drug into the bloodstream.
- Abbott's market crisis: Batches of drug decreasing, and Form 2 was showing up in all capsules.

# Case Study: Ritonavir

- This required a new process to make Form I and a new formulation to make Form II effective.
- The experience sent a strong message to the industry about controlling the crystallisation process.
- Abbott was forced to remove Ritonavir from the market until they solved the problem, resulting in a huge loss of profits.

# Case Study: Ritonavir

- Abbott's patent problem: As the company moved to patent Form II, the European Patent Examiner indicated that Form II was unpatentable on the basis of inventive step. The EPO requested Abbott to “submit relevant comparative tests which should demonstrate [...] improved pharmacological properties and/or an unexpected advantage”

# Case Study: Ritonavir

- Abbott argued that non-obviousness was sufficient to show inventive step, and that Form II had a different property. Therefore, according to Abbott, a pharmacological advantage was not required.
- Abbott relied on T 154/87, a case that held “the achievement of a surprising effect is no precondition for the existence of inventive step”.
- The company further argued that the property of stability was unexpected. The patent was ultimately granted.