Intellectual Property and crystalline forms

How to get a European Patent on crystalline forms?

Ambrogio Usuelli
Chief-Examiner
European Patent Office, Munich, Germany

Bologna, 19th January 2012

Sponsor: the European Patent Academy of the EPO

The author has taken all reasonable care to ensure that the content of the presentation is accurate. The opinions of the author expressed herein do, however, not necessarily state or reflect those of the EPO, and no responsibility can be taken for the consequences of error.
Today’s Presentation

- What is a patent?
- Patentability requirements
- Solid State and I.P./ Background
- Patentability issues (with particular reference to polymorphs)
  - Clarity (Article 84 EPC)
  - Disclosure (Article 83 EPC)
  - Novelty (Article 54 EPC)
  - Inventive Step (Article 56 EPC)
  - Unity (Article 82 EPC)
**What is a patent?**

- **A patent is an *exclusive* right**
  - It does **NOT** GIVE the right to **do**
  - It **GIVES** the right to hinder by law others from doing what you have invented

- **A patent / patent application comprises two parts**
  - the **description** which describes what was known before and, in a detailed manner, what is the invention
  - the **claims** which determine the scope of protection, what the inventors consider to be their invention for which they seek property

- optionally, the application may also comprise **figures** (spectra etc.)
What is a European Patent?

- A European Patent is a Patent **centrally** granted by the European Patent Office
  
  - the E.P.O. exists since 1978

  - the European patent has the same effect as a National Patent in any of the 38 Member States of the European Patent Organisation

  - after its grant, a European Patent is transformed into a bundle of national patents, all having an independent life and fate

  - the EP system is characterised by a **single procedure** finally resulting in **several patents**

- The European Union Patent - Unitary Patent
  
  - does not exist yet

  - it will be granted by the European Patent Office

  - it will be unique and valid for the whole territory of the E.U,

  - characterised by a **single procedure** finally resulting in a **unique patent**
**Procedure for obtaining a European patent**

- A European Patent application is first subjected to a **documentary Search**

- Then, it is submitted to **substantive examination** by patent examiners from the European Patent Office

- The **main criteria** for patentability are:
  - the invention must be **novel**
  - the invention must be **sufficiently disclosed**
  - the invention must involve an **inventive step**

- In addition, there are **other requirements** for the patent application
  - the invention must be claimed in a **clear** manner
  - the claims must rely upon a **single inventive concept** only
Background: solid state inventions at the E.P.O.

- In recent years the E.P.O. has received an increasing number of applications directed to solid state forms of chemicals, in particular of active pharmaceutical ingredients (APIs), particularly on polymorphic forms.

- At the E.P.O. approximately 80 examiners work on a very regular basis on files relating to solid state applications.
  - There is an ongoing policy dating back at least 5 years to harmonise examination practice.
  - To keep examiners up to date with technical developments in this field.
    - In house lectures & participations to conferences & workshops.

- There is some case law relating specifically to solid state applications, but not much.
  - The practice is mainly based on a consistent approach developed within the E.P.O., sometimes in cooperation with certain other patent Offices (e.g. China, Japan).
Disclosure of the Invention (Article 83 EPC)

• "The European patent application must disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art."

(Article 83 EPC)

• The information in the application must allow the skilled person, using his common general knowledge, to perform the invention
  – over the whole claimed area
  – without undue burden and
  – without needing inventive skill

(cf. Guidelines 2007, C-II, 4.9)
Disclosure and solid state inventions

Lack of sufficient disclosure may typically arise if:

- the application does not clearly describe the method used to determine the parameters of the claimed solid state form (cf. Guidelines 2007, C-II, 4.10)
- the preparation processes disclosed in the application are identical to those of the prior art, but a different solid state form is allegedly obtained which is hardly plausible
- all preparation processes in the application involve seeding, but the preparation of the seed crystals is not described

Disclosure problems may be prevented by
- detailed examples
- identification of essential features (critical parameters)
Disclosure: Decision T 1066/03

Ω Invention: a process for preparing amorphous atorvastatin (hemi calcium salt) from the crystalline form I

Ω Facts:
- crystalline form I was nowhere described up to the filing date and the examples in the description used seed crystals
- the application did not explain how to obtain the seed crystals

Ω Decision:
- the patent was revoked in opposition proceedings for lack of disclosure
- the Board of Appeal confirmed the revocation
Disclosure of the invention - remarks

General considerations:

- a certain, **limited amount of trial-and-error can be accepted** if the skilled man is given enough information in the application

- the **more detailed** the examples, the **easier** is it for the skilled man to carry out the invention over the claimed area

- **hiding essential features** which a skilled man cannot deduce from the application documents or from general knowledge will lead to a refusal/revocation

- "solid form" inventions require a **very complete disclosure**
Novelty (Article 54 EPC)

"(1) An invention shall be considered to be new if it does not form part of the state of the art.

(2) The state of the art shall be held to comprise everything made available to the public by means of a written or oral description, by use, or any other way, before the date of filing of the European patent application."

(Article 54(1) and (2) EPC)
Novelty: parameters and decision T 296/87

- In most cases, crystal forms are defined in a claim by parameter values

- Decision of the Technical Board of Appeal T 296/87 states:

  "a chemical substance is held to be new if it differs from a known substance in a reliable parameter"
Novelty: enabling disclosure

• In the examination of novelty the claimed invention is compared with the content of each prior art document.

• To challenge novelty a prior art document must be enabling.

• The Guidelines 2007, C-IV, 9.4:

  "... a chemical compound, the name or formula of which is mentioned in a prior art document, is not thereby considered as known, unless the information in the document, together, where appropriate, with the knowledge generally available on the relevant date of the document, enables it to be prepared and separated ..."

  - This may apply if a prior art document discloses the analytical data of a crystal form but no information for its preparation.
**Novelty: implicit disclosure and parameters**

- The Guidelines 2007, C-IV, 9.6:

  "It may happen that in the relevant prior art a different parameter, or no parameter at all, is mentioned. If the known and the claimed products are identical in all other respects then in the first place an objection of lack of novelty arises."

  - this would apply if the prior art already discloses the same compound as the claimed crystal form also in crystalline form
  
  - comparative data are then usually required to establish novelty
Novelty: implicit disclosure and parameters

• When the applicant is invited to provide an experimental proof that the compound claimed is different from the compound of the prior art...

...it should also be made clear that the parameter compared is one of the parameters included in the claim of the invention under examination

Clearly: a good documentary search before filing a patent application is of great help
Novelty: implicit disclosure and parameters

Example:

• **Claim 1**: "Crystalline form of compound X having a melting point 100°C"

• **Prior art**: Crystalline form of compound X having an X-Ray diffraction pattern as depicted in Fig. 1. Crystallization process very similar to the one of the application under examination.

• The applicant should provide the melting point of the prior art compound.

• Comparing the X-Ray diffraction pattern of the two compounds is not appropriate because it could happen, at least in principle, that two compounds have different X-Ray spectra but the same melting point.
Novelty: Decision T 885/02

- Claim 1 of granted patent EP-B-0 970 955:
  "1. Paroxetine methane sulfonate in crystalline form having *inter alia* the following characteristic IR peaks: 1603, 1513, 1194, 1045, 946, 830, 776, 601, 554, and 539 ± 4 cm\(^{-1}\); and/or the following characteristic XRD peaks ... ."

- Document D1: preparation of crystalline paroxetine mesylate, which was characterized by the following list of IR peaks:
  3023, 2900, 2869, 2577, 1615, 1515, 1500, 1469, 1208, 1169, 1100, 1038, 962, 931, 838, 777, 546, and 531 cm\(^{-1}\).
Novelty: Decision T 0885/02

- The peak lists in claim 1 and in D1 are not identical. This, however, does not mean that the two crystalline forms are therefore different since the list of peaks are not limitative.

- Peaks of the high-frequencies region of the IR spectrum (> 2000 cm\(^{-1}\)) are absent in claim 1 but were considered important to distinguish polymorphs. The Board of Appeal was therefore not convinced that the peaks in claim 1 are the relevant peaks for distinguishing polymorphs of paroxetine mesylate.

- Novelty of claim 1 vis-à-vis D1 was denied.
"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."
Inventive Step: Decision T 777/08

Ω Invention: Crystalline Form IV of atorvastatin hydrate characterized by the following X-Ray powder diffraction pattern...

Ω Facts:

- The most relevant prior art documents disclosed the amorphous form of atorvastatin

- The board acknowledged the novelty of Form IV

- Inventive Step: experimental report of the patentee showing shorter filtration and drying times for form IV compared to the amorphous form.
Inventive Step: Decision T 777/08

According to the BoA the objective technical problem can be defined as follows:

*Provision of atorvastatin in a form having improved filterability and drying characteristics*

Solution of the problem: Form IV

OBVIOUS or INVENTIVE?
Inventive Step: Decision T 777/08

Considerations made by the board:

The skilled person would have been aware of the fact that instances of polymorphism were commonplace in molecules of interest to the pharmaceutical industry...

... it belonged to the routine tasks of the skilled person involved in the field of drug development to screen for solid-state forms of a drug substance...

...in the absence of any technical prejudice and in the absence of any unexpected property, the mere provision of a crystalline form of a known compound cannot be regarded as involving an inventive step.
Improved **filterability and drying** characteristics of form IV can be regarded as **unexpected properties**?

**What is known about amorphous and crystalline forms?**

D27: several disadvantages can be expected for the amorphous form with respect to chemical and physical stability.
Inventive Step: Decision T 777/08

What is known about amorphous and crystalline forms?

D28: Crystalline products are generally the easiest to isolate, purify, dry and, in a batch process, handle and formulate
In view of his general knowledge, the skilled person starting from the amorphous form, would have a clear expectation that a crystalline form thereof would provide improved filterability and drying characteristics.

Although this might not be true of every crystalline form it was nevertheless obvious to try this avenue with a reasonable expectation of success.

Decision: Form IV is not inventive
Thank you for your attention!

Acknowledgements:

- Sponsored by the European Patent Academy of the EPO
- Thanks to:
  - Bertrand Gellie Director dept. 2101
  - Marc Gettins & Claire Johnson for revision and suggestions

Copyrights: EPO January 2012