Inventive step of alternative polymorphs/solvates/salts of drug compounds

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Polymorphs/solvates/salts of drug compounds

Technical difference with regard to the prior art

Prior art:
Form A (polymorph/solvate/salt) of active compound X

Invention:
Form B (polymorph/solvate/salt) of active compound X
Polymorphs/solvates/salts of drug compounds

Technical problem to be solved

In case where unexpected/surprising effects for B in comparison to A cannot be demonstrated, the problem to be solved has to be seen in the provision of an alternative form.

Acknowledgement of inventive step possible?
Frequent objections raised by the EPO against inventive step of claimed alternative forms:

- The crystalline forms/solvates/salts A and B are functionally equivalent and they have the same biological/medicinal properties.

- The skilled person expects the crystalline forms/solvates/salts A and B to have the same activity.

- The use of different crystalline forms/solvates/salts is common practice.

- The systematic investigation of a compound to determine whether it is prone to polymorphism is routine practice in the pharmaceutical industry, and methods of screening for polymorphs are well-known in the prior art.

- Since such a routine and daily work in the pharmaceutical industry is expected to yield novel crystalline forms/solvates/salts, the provision of B is an obvious solution of the problem to provide an alternative form.
T 777/08: When is a polymorph inventive?

- The skilled person in the field of pharmaceutical drug development is aware of the fact that instances of polymorphism were commonplace in molecules of interest to the pharmaceutical industry.

- The skilled person knows it to be advisable to screen for polymorphs early on in the drug-development process.

- The skilled person is familiar with routine methods of screening for polymorphs by crystallization from a range of different solvents under different conditions.
T 777/08: When is a polymorph inventive? (continued)

• Consequently, 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 pharmaceutically active compound cannot be regarded as involving an inventive step.

• The arbitrary selection of a specific polymorph from a group of equally suitable candidates cannot be viewed as involving an inventive step.
T 777/08: When is a polymorph inventive? (continued)

- Frequent view of patent practitioners:
  
The inventiveness of a novel polymorphic form of a pharmaceutically active compound will be acknowledged only if the novel polymorphic form is associated with an unexpected effect/activity.

- Is it so?
  
  No, not necessarily!
One opportunity for the inventive step of an alternative form

To be shown:

- How to obtain the polymorph/solvate/salt B was not obvious to the person skilled in the art.
- The claimed polymorph/solvate/salt B could not be found by the skilled person using routine screening.
- An inventive activity is required to manufacture the polymorph/solvate/salt B.
This opportunity can be deduced from Atorvastatin T 777/08:

- The claimed subject matter was a **crystalline** form of Atorvastatin, and the **prior art** disclosed the **amorphous** form.

- The decision that the crystalline form was obvious was made under the assumption that the claimed polymorph was found by the person skilled in the art using routine screening.

Closer look at the decision!
This opportunity can be deduced from Atorvastatin T 777/08 (continued):

• With regard to routine screening T 777/08 makes reference to the known decision tree for the discovering of polymorphs/solvates:

• The first step is to crystallize the substance from a number of different solvents in order to attempt to answer the question of whether polymorphs are possible.

• The solvents should include those used in the final crystallization steps and those during formulation and processing and may also include water, methanol, ethanol, propanol, isopropanol, acetone, acetonitrile, ethyl acetate, hexane and mixtures, if appropriate.

• With regard to the flowchart for solvates, it is outlined that the crystallizations are essentially the same as in the polymorph decision tree, but should additionally include solvent-water mixtures in order to maximize the chance for hydrate formation.
A practical case study

• The Claim:
  • Crystalline form III of *the hydrochloride salt of a drug compound* having a X-ray powder diffraction pattern (CuKα radiation) comprising characteristic peaks of 4.1, 12.3, 16.5 and 17.4 ± 0.2 degrees 2θ.
A practical case study (continued)

• The facts:
  
  • Form III is obtained by recrystallization from pyridine.
  
  • Pyridine was not used in the final preparation (crystallization) step for the hydrochloride salt of the drug compound in the prior art and was also not used during formulation and processing thereof.
  
  • Pyridine also does not fall under the specific solvents as mentioned in the decision tree of T 777/08 for polymorphs/solvates.
  
  • Experiments show that when using different solvents such as water/methanol, form III is not obtained.
A practical case study (continued)

- **Argumentation for the inventive step of Form III:**
  - The prior art does not provide any information regarding processes which might be used for the preparation of form III.
  - No hints derivable from the prior art that the recrystallization from a specific solvent (pyridine) results in a novel crystalline form III.
  - Form III is not obtained by routine screening or standard methods.
  - There is no path which could lead the skilled person to form III in an obvious way.
A practical case study (continued)

- Argumentation for the inventive step of Form III (continued):
  - With regard to the non-obviousness of the claimed form III, the deciding factor is not whether the person skilled in the art would have expected that form III has the same biological/medicinal properties as the polymorphs of the prior art, but whether it was obvious for the person skilled in the art how to make form III available.
  - To acknowledge inventive step, it is not necessary to show that the specific form III leads to an unexpected effect.
  - The case law of the Boards of Appeal does not exclude inventive step for a specific form of an active agent without showing an unexpected effect, but only representing a non-obvious alternative.
Case law of the Boards of Appeal: Inventive step of alternatives

T 0092/92, Item 4.5 of the Reasons of the Decision:

• Article 56 EPC does not require that the problem to be solved should be novel in itself and no ground can be seen why a novel alternative solution to a known problem should be excluded from patentability for a lack of inventive step for the reason that the problem has already been solved in a different manner.
Case law of the Boards of Appeal: Inventive step of alternatives (continued)

T 0780/94, Item 4.1 of the Reasons of the Decision:

- The fact that the problem as such is not novel in itself does not exclude patentability of an alternative solution if a new solution fulfills the requirements of the EPC.
Case law of the Boards of Appeal: Inventive step of alternatives (continued)

T 0323/03, Item 2.7 of the Reasons of the Decision:

- Even though the presence of a technical advantage may serve as a basis for defining a technical problem in an objective manner and therefore may be an indication of the presence of inventiveness, its absence is not sufficient for deciding that the claimed subject matter lacks inventive step. This situation may rather request the investigation of the technical problem and subsequently the determination of the so-called objective technical problem. This could be, for example, the finding of an alternative solution to a technical problem already solved according to the state of the art. An invention in fact may also lie in the provision of an alternative which brings about comparable results to the starting point for the evaluation of inventive step.
Back to the practical case study

- **Decision:**
  - Form III represents a non-obvious alternative to the known crystalline forms of the prior art.
  - Inventive step is acknowledged for Form III.
Summary and conclusions:

• An inventive step is to be acknowledged in cases where the claimed polymorph/solvate/salt cannot be deduced in an obvious way from the prior art and also does not belong to the forms which are obtained by routine screening or standard methods.

• In such a situation, it is not required that the claimed polymorph/solvate/salt shows unexpected properties/activities over the known forms in the prior art.
Thank you for your attention!

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