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EPO RULING ON INVENTIVENESS OF DRUG POLYMORPHS

On May 24, 2011, the EPO Technical Board of Appeal (TBA) 3.3.01 handed down decision T777/08 concerning the inventiveness of (specific) polymorphic forms of a drug previously only known in solid amorphous form. This decision caused considerable attention in the pharmaceutical industry.

The relevant claimed subject matter of European Patent EP 1 148 049 relates to crystalline forms II and IV of the statin drug atorvastatin hydrate that are characterized by an X-ray powder diffraction pattern expressed in terms of 2θ angles, d spacings, and relative intensities with a relative intensity of $>15\%$ determined using $\text{CuK}\alpha$ radiation.

An opposition was filed against the grant of the patent that finally resulted in the revocation of the patent in its entirety due to the lack of inventive step.

The EPO Opposition Division (OD) identified two closest prior art documents, each disclosing solid amorphous forms of atorvastatin obtained from re-crystallization processes, and considered the problem to be solved in the provision of further crystalline forms of atorvastatin having surprising effects as compared to the prior art. The OD did not consider the comparative data provided to be pertinent since the solid-state form chosen for comparison was the amorphous form rather than the crystalline form. Moreover, the OD argued that, even were the amorphous form to be accepted as a valid point of comparison, an inventive step could not be based on the comparative data provided, since the skilled person would expect improvements in stability, filtration and drying with crystalline forms as compared to amorphous forms.



The patentee lodged an appeal against this decision. In his view, the specific polymorphs claimed are characterized by improved filterability and drying. The patentee continued to argue that it was part of the general knowledge of the skilled person that amorphous forms were generally more soluble and bioavailable than their crystalline counterparts. Therefore, the skilled person would have no incentive to look to the latter as alternative forms of the drug having the above specificities. Based on the cited prior art, the skilled person could not have predicted that the polymorphs claimed would show the improved properties demonstrated, which made them more amenable to large-scale processing. Hence, inventive step were to be acknowledged. Notably, original disclosure and novelty were not contested during the appeal proceedings.

The competent TBA confirmed that the objective technical problem to be solved by the claimed drug polymorphs could be seen in the provision of an alternative form of atorvastatin having improved filtration and drying properties. That this problem actually was solved by the claimed polymorphs was also not contested during the appeal proceedings. However, the TBA found the claimed solution to be obvious for the skilled person based on common knowledge at the priority date of the patent and thus non-inventive.¹

The major source of information for determining the common knowledge was a review article published shortly before or after the priority date (the exact publication date could not be established). The TBA held that irrespective of the exact publication date the article in any case would reflect the skilled person's knowledge at the time before the priority date of the patent in suit and thus would be a legitimate basis for evidence of common general knowledge (following decision T1110/03, cf. headnotes 1 and 2).

Further considering two additional prior art documents confirming the teaching of the review article that Board came to the conclusion that at the priority date of the disputed patent it was general common knowledge that:

- (i) polymorphism is commonplace in molecules of pharmaceutical interest;

¹ Cf. T777/08, point 5.1 of the reasoning.



- (ii) early screening for polymorphs is advisable in a drug development process; and
- (iii) crystallization from different solvents under different conditions is a routine method for screening for polymorphs. Several disadvantages can generally be expected for the amorphous form, namely, with respect to their chemical and physical instability.²

Accordingly, the Board ruled that, at the priority date of the patent in suit, the skilled person in the field of pharmaceutical drug development would have been aware of the fact that instances of polymorphism were commonplace in molecules of interest to the pharmaceutical industry, and have known it to be advisable to screen for polymorphs early on in the drug development process. Moreover, he would be familiar with routine methods of screening. 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.³

Furthermore, the TBA pointed out that the technical effect achievable by crystalline polymorphs was known, as explicitly stated in another prior art document considered documents: crystalline products are generally the easiest to isolate, purify, dry and, in a batch process, handle and formulate. As a consequence, a skilled person would attempt obtaining a crystalline form, rather than an amorphous form, in order to achieve the improved filtration and drying properties.

Hence, when starting from the amorphous form of a pharmaceutically active compound as closest prior art, the skilled person would have a clear expectation that a crystalline form thereof would provide a solution to the problem of providing a product having improved filterability and drying characteristics. The arbitrary selection of a specific polymorph from a group of equally suitable candidates cannot be viewed as involving an inventive step.⁴

² Cf. T777/08, point 5.2 of the reasoning.

³ Cf. T777/08, headnote 1.

⁴ Cf. T777/08, headnote 2.



Finally, the TBA outlined that the skilled person in the field of drug development would not be dissuaded from attempting to obtain a crystalline form by the prospect of a potential loss of solubility and bioavailability when compared to the amorphous form, but would rather regard this as being a matter of trade-off between the expected advantages and disadvantages of these two classes of solid-state forms.⁵

Thus, in the Board's view, the provision of crystalline polymorphs that do not achieve anything more than the obvious advantages of crystalline materials over amorphous ones is not based on an inventive step. This would apply for the provision of polymorphs in general as compared with amorphous forms, and also for the It is also of note that the present ruling parallels established EPO case law concerning the patentability of enantiomers (cf. inter alia T296/87, T1048/92, and T1046/97).

Hence, it is to be expected that inventive step of a novel polymorph form of a pharmaceutically active compound will only be acknowledged if the novel polymorph form is associated with an unexpected pharmaceutical activity, while improved physical and/or physicochemical properties would not be sufficient. Also, an inventive step might be acknowledged if inventive skills are required to manufacture the polymorph.

⁵ Cf. T777/08, headnote 3.