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Tips and tricks on how to obtain patent protection for polymorphs

COHAUSZ & FLORACK

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Tips and tricks on how to obtain patent protection for polymorphs

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Introduction

Chemical compounds, if present as solids, may occur in different amorphous forms or in different crystalline modifications. Such polymorphs can be of importance in the pharmaceutical sector as regulatory authorities often tie regulatory approval to a single specific polymorph.

Obtaining patent protection for a polymorph in addition to a primary compound patent may be particularly advantageous, especially if filed successively, as the polymorph patent may add extra time to the patent protection for the modification of an approved drug or a clinical candidate. The polymorph patent offers the same scope of protection as a product patent and, therefore, offers certain advantages compared to other secondary patents (eg, second medical use patents).

Drafting and prosecuting patent applications for polymorphs can be an art in itself, even though basically the same patent law requirements apply as for other patents. The following analysis is mainly based on our experiences in prosecuting polymorph patent applications before the European Patent Office but may be applicable in a large part also before other patent offices.

What is a polymorph?

The same solid compound may occur in different modifications, for example, in an amorphous form (only locally formed crystal-like structures with no long-range order of atomic positions) or in a crystalline state (atomic positions with long-range order forming a crystal lattice).

However, this does not mean that the compound may only exist in these two solid-state forms: for example, if there are at least two distinguishable crystal structures, the skilled person talks about 'polymorphs'. Moreover, scientists also call the occurrence of different amorphous forms 'polyamorphism' (O Mishima and E Stanley, *Nature* 1998). Solvates and hydrates of compounds are also often treated as polymorphs ('pseudopolymorphs').

What is so special about polymorphs?

Polymorphs are unique because different modifications may have different physico-chemical properties. Hence, a polymorph may be specifically selected for certain applications based on its most suitable physico-chemical properties. This strategy is especially important when formulating a drug or when seeking to optimise production or storage stability. Evaluating and tightly controlling processing conditions such as temperature, agitation or solvent compositions are very relevant in obtaining the desired polymorph.

Even though the solid polymorphs may display different properties (eg, different melting points, solubilities or stabilities), no differences exist once the polymorph is in solution. That is why a solution of different solid modifications shows the same type of biological activity. However, the extent of biological activity may still differ; the reason for this can be, for example, divergent release rates of the individual polymorphs. If the polymorphs differ in their degradation rate during production or storage, the amount of active compound being provided in the dosage form may differ, too.

All of this shows why regulatory authorities usually require applicants to provide information about the polymorphic form. It also explains why pharmaceutical companies invest so much of their research and development effort into finding a crystalline structure that is optimal and does not interconvert

into another polymorphic form. Patent protection for a polymorph is often crucial for companies to secure this extra effort, transform it into a competitive advantage and try to recoup the high research and development costs that have already been incurred for finding a new drug candidate.

What are the particularities to be observed when drafting and prosecuting a polymorph patent application?

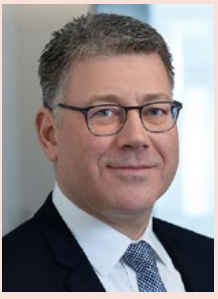
When drafting a patent application for a polymorph, it is crucial to sufficiently characterise the different modifications and to clearly distinguish the polymorphic forms in the application, particularly in the claims, to fulfil the clarity and sufficiency of disclosure requirements set by patent offices. The burden of proving that the invention may be repeatedly performed and properly reproduced lies with the applicant.

Usually, the patent claims in a polymorph patent characterise the polymorph by way of parameters (eg, peaks of a diffractogram). The most commonly used solid-state technique to differentiate between polymorphs is X-ray powder diffraction (XRPD), which not only provides a measure for qualitative identification but also for quantitative analysis if mixtures of polymorphs are examined.

However, single-crystal X-ray analysis (providing the highest level of information, including stereochemical properties), infrared spectroscopy, Raman spectroscopy, solid-state nuclear magnetic resonance spectroscopy, thermogravimetric analysis, differential thermal analysis and differential scanning calorimetry can also be suitable measures to characterise a polymorph.

The latter methods may also be useful to complement XRPD data, especially when crystallographic peaks are overlapping or close together in the diffractogram or when a further clear distinction from the prior art is necessary during prosecution.

As parameters in general may vary depending on the experimental set-up, details of the applied methods, in particular information on internal and external standards and measurement parameters, should be indicated in the application. Methods in general should be described in the patent specification or need to be known from the prior art (which can be specifically referenced). Also in the patent claims, the applied measurement method should be at least indicated if parameters are used to characterise the polymorph.



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Article 83 of the European Patent Convention (EPC) requires patent applications to disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art. Lack of sufficient disclosure can not only lead to a refusal of an application during examination, but also forms a powerful ground of revocation when competitors attack polymorph patents in post-grant opposition proceedings (Article 100 (b), EPC).

Sufficiency of disclosure must be fulfilled at the filing date of the patent application. Thus, clear and complete information on the relevant experimental process parameters to obtain and characterise the polymorph should be included in the application on the date of filing, because an insufficient disclosure objection cannot be remedied later on during patent examination or opposition proceedings. In other words, parameters such as solvents and temperature should be indicated in the application at

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the date of filing to avoid any sufficiency of disclosure objections in the future.

What can different claim formats for protecting polymorphs look like?

In addition to product claims for a polymorph, which will usually need to recite one or more of the above-mentioned parameters, product-by-process claims may serve as a valuable alternative or complementary way to clearly claim the polymorph by a highly reproducible and even more distinct process. They are usually worded in the format: "Polymorph of compound X obtainable by process Y comprising the steps of". The polymorph as such must be novel, as product-by-process claims are not rendered novel merely by the fact that the product is produced by means of a new process.

Claims for methods of preparing the polymorph should also be included as they complement the product claims and can form important fallback positions.

First and second medical use claims may be possible for polymorphs if the use as a medicament or the therapeutic use is unknown from the prior art and is plausible from the application as filed. But whether medical use claims are allowable and in what form they need to be presented may strongly depend on the specific jurisdictions.

Objections during examination or post-grant proceedings

As mentioned, basically the same requirements apply to polymorph patents as for other patents. Hence, they also need to comply with the clarity, unity of invention, added subject matter, novelty and inventive step requirements.

Unity of invention objection

Even though product claims directed to different polymorphs of the same compound may seem closely related and may seem to fulfil the requirements of "forming a single general inventive concept", whether this is actually the case depends on the form disclosed in the prior art (ie, an amorphous or a crystalline form).

Therefore, there is a risk that different claimed polymorphs may be treated as different inventions.

For polymorphs, inventive step is usually the most difficult hurdle to overcome, as some jurisdictions such as the EPO may consider the mere screening for polymorphs to be a routine operation of the skilled person

A unity objection can be overcome by restricting the claims to a specific polymorph. As usual, divisional applications may be filed to additionally obtain protection for the other originally claimed polymorphs.

Added subject matter objection

A further patentability requirement is the prohibition of added subject matter.

Even though mainly the same standards apply, when drafting and prosecuting a polymorph patent application, as compared to other types of patent applications, one should be aware that there might be some very particular obstacles.

For example, if a patent office follows a strict and literal approach when determining added subject matter (as is the case at the EPO), it can be problematic if the claimed subject matter contains a set of significant peaks selected from an X-ray diffraction pattern that is only disclosed as a full XPRD spectrum or as a complete list of XPRD peaks. Hence, it is advantageous to include a dependent claim, a preferred embodiment, a figure or a list that discloses a subset of the peaks of interest to prevent the later claimed selection of peaks from extending beyond the content of the application as filed.

Novelty

A polymorph lacks novelty if the polymorph itself is disclosed in the prior art either by explicit description or implicitly, for example, by a prior art disclosure of a preparation method that inevitably leads to the claimed polymorph. The burden of proof lies with the applicant to evidence by comparative tests that a process of the prior art does not inevitably result in the claimed polymorph or that a known form differs from the claimed polymorph in a reliable parameter.

Furthermore, the general principles of novelty assessment usually also apply to polymorph cases such that, for example, a generic prior art disclosure of "a compound or polymorphs thereof" does not anticipate a specific polymorph and that only enabling disclosures of polymorphs or their preparations can be detrimental to novelty. Where mixtures of polymorphs are concerned, novelty assessments can become even more complex.

Inventive step

For polymorphs, inventive step is usually the most difficult hurdle to overcome, as some jurisdictions such as the EPO may consider the mere screening for polymorphs to be a routine operation of the skilled person. Further, an arbitrary selection of one polymorph of a group of equally suitable polymorphic candidates may not be regarded as involving an inventive step.

The assessment of inventive step may also highly depend on which document is considered to be the closest prior art. This is usually the document that relates to the same or the most closely related technical purpose. In a second step, the document with the most similar compounds, process steps and/or intermediates is usually chosen.

For instance, if an application for the first time discloses and claims a polymorph, the closest prior art may be the same compound in a crystalline form for the same technical use or, if several polymorphs are already known, the polymorph with the most similar features relevant for the technical use.

To establish a technical effect based on the distinguishing features, the application should ideally already contain comparative data on the same target property as in a relevant prior art document. The application as filed should at least make the technical effect plausible.

If this is the case, applicants can also rely on data generated and submitted after the filing date to fur-

ther support the technical effect in relation to the EPO. Ideally, the technical effect should be unexpected or an improved effect in light of and compared to the prior art. Effects that are often taken into account in polymorph cases are improved stability or solubility. Care should be taken to provide experimental data of the claimed polymorph in comparison to the 'right', or in other words, closest prior art form, not just any form of the compound described in the prior art (T 0912/06).

If an unexpected effect or advantage over the closest prior art is sufficiently demonstrated by evidence, this improved effect can be included in the formulation of the objective technical problem.

The unexpected effect or advantage of the claimed polymorph should not be offset by disadvantages in other respects or by a contradicting disclosure, as the polymorph's effects should exceed the prior art's performance ideally as a whole. It is crucial that the type of effect is unexpected and cannot be foreseen with a reasonable expectation of success by the skilled person based on the prior art or common general knowledge. The EPO Boards of Appeal have denied an inventive step in cases in which the polymorph turned out to be an arbitrary selection from a group of equally suitable candidates. A key case in this respect is T 777/08, which concerned a particular crystalline polymorph (Form IV) of atorvastatin hydrate. According to T 777/08 (Headnote I), the skilled person:

> *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.*

According to T 2007/11, mere speculative and conclusory statements of technical effects without supportive data will hardly be acceptable to support inventive step of a polymorph (see reasons, 7.7.2).

If applicants are not successful in establishing a special technical effect over the closest prior art, the EPO might reformulate the objective technical problem as being the provision of a mere alternative form. However, this should be avoided by all means as the result is usually a finding of obviousness based on the argument that the screening for and identification of alternative polymorphs is a routine operation for the skilled person. In very rare cases it might still be possible to show that standard or routine measures would not have led to the claimed polymorph in any obvious way, so that even a mere alternative can be inventive.

Conclusion

Solid-state inventions are basically not different from any other invention as far as the requirements of patentability are concerned. However, there are some specific obstacles that should be well taken care of: for example, having a thoroughly elaborated analysis based on several methods to clearly and completely characterise a polymorph and to sufficiently distinguish the polymorph from other polymorphs.

In addition, to avoid any added subject matter objections during prosecution, the polymorph's parameter should be gradually disclosed. As always, to be inventive over the prior art, it must be made plausible in the application that the polymorph displays an unexpected effect that distinguishes it from the amorphous and/or other crystalline forms of the prior art so that the claimed polymorph is not merely seen as an arbitrary selection from equally suitable candidates. Having a secondary patent with the scope of a compound patent and extended patent lifetime can be rewarding for patent owners as an additional basis to enforce their rights against patent infringers.

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