Patenting Polymorphs at the European Patent Office

Obtaining patents for polymorphs can be challenging. However, before the European Patent Office, there is no general rule which makes polymorphs less patentable in principle than other subject matter. With careful drafting and consideration of any specific advantages associated with the polymorph of interest, European patents directed to polymorphs of commercial significance can be obtained. Such patents can act as additional barriers to entry of generic products onto the market, and can thus be very useful in managing the life cycle of a patent estate for pharmaceutical and other biologically active compounds.

Introduction

A solid form of a small molecule may be amorphous (when there is no long range order in the orientation of the small molecules) or crystalline (when the small molecules are arranged in a periodic crystal structure). Many small molecule pharmaceutical compounds exist in a number of different crystalline forms, often known as polymorphs. Different polymorphs typically have different properties and those properties must be understood during the development of a pharmaceutical compound. The identification and assessment of the available polymorphs of a pharmaceutical compound is therefore an important area of drug development.

There are certain considerations which should be taken into account when drafting and prosecuting patent applications for new polymorphs of known compounds. Four key considerations are: (i) what is the invention; (ii) how to claim the polymorph; (iii) how to avoid allegations of inherent anticipation; and (iv) demonstrating inventive step. These matters are discussed in turn below.

What has been invented?

It is generally important to devise an appropriate strategy for patenting a polymorph from the outset, particularly regarding the advantages associated with the polymorph of interest. The reason for this is that carrying out polymorph screens can be considered to be a routine task. Consequently, a patent application which simply claims all, or even most, of the polymorphs identified in a screen, without indicating why any of the claimed polymorphs solves a technical problem, is likely to be challenging to prosecute.

It is fairly common for a number of distinct inventions to arise from a polymorph screen. Each invention typically arises from the identification of a single polymorph with a particular advantage not observed for other polymorphs of the same compound. It is generally advisable to file a separate patent application for each distinct invention identified, since this tends to result in a clearer narrative on the advantages associated with the claimed polymorph and often makes it easier to establish inventive step.

How to claim polymorphs

As with any invention, an independent claim for a polymorph should be drafted such that the key features of the invention are captured while excluding the prior art. Dependent claims should also be included which provide flexibility to amend the independent claims, in the event that objections are raised during prosecution. Some specific considerations which apply to polymorphs are considered below.

It is in principle possible to define a polymorph structurally in terms of the spatial arrangement of the atoms and molecules within a crystal lattice. In practice, however, polymorphs are usually characterised by reference to their properties as determined using spectroscopic and analytical techniques. Common techniques used to differentiate between different polymorphs are:

- x-ray powder diffraction (XRPD);
- single crystal x-ray analysis;
- Fourier transform infrared spectroscopy (FTIR);
- Raman spectroscopy;
- differential scanning calorimetry (DSC); and
- thermogravimetric analysis (TGA).

One or more properties of a polymorph as measured by these techniques may be used to characterise a polymorph in a claim. The powder diffraction pattern of a polymorph as obtained by XRPD is the most commonly used parameter for defining a polymorph. An XRPD pattern contains a number of peaks at specific 2θ values. The exact distribution of peaks is generally unique to a specific polymorph and may therefore be used to distinguish that polymorph from other polymorphs. Of greatest importance for characterising a polymorph by XRPD are the highest intensity peaks found at lower 2θ values.

When using XRPD peaks in a claim, it is important to bear the following in mind.

- 2θ values are dependent on the wavelength of x-rays used to measure the XRPD pattern. It is therefore important that the patent application clearly states the x-ray wavelength used. In the absence of a wavelength, a claim is in danger of being found to lack clarity or sufficiency because the skilled person would be unable to determine whether or not a given solid form has the required peaks as measured by XRPD. Although it is not essential to include the wavelength in the main claim when filing the application, European examiners often require during examination that the claim be amended to recite the wavelength ("*… as measured using an x-ray wavelength of 1.5406 Å*"). Accordingly, it is advisable to provide word for

word basis for such an amendment in the description.

- Only the most important peaks should be included in the main independent claim. This may for instance be two, three or four of the highest intensity peaks in the XRPD pattern. The most important peaks for defining a specific polymorph are often those found in the fingerprint region of the XRPD pattern (typically at from 5° 2θ to 20° 2θ). Inclusion of too many peaks in the main independent claim may limit the enforceability of a resulting patent. Additional peaks should be included in dependent claims in case they are required to further distinguish over another polymorph.
- 2θ values should typically be stated to one decimal place. Although the output of XRPD machines often contains values to a large number of decimal places, it is preferable in a claim to allow for experimental variation by only including a limited number of significant figures.
- The presence of experimental variation should also be allowed for by including an error margin in the stated 2θ values. This is typically ±0.2° 2θ. It is advisable to include a narrower error range (e.g. ±0.1° 2θ) as a fall back in the description.
- XRPD analysis typically provides relative peak intensities in addition to peak locations as defined by 2θ values. These peak intensities can in some cases be useful for further defining the invention. However, peak intensities can depend on a number of factors, including experimental preparation, and should not therefore be included in the main independent claim.

Taking these considerations into account, a main independent claim for a polymorph worded in a form suited for European practice may be as follows (with illustrative values).

A crystalline form of [compound] having an x-ray powder diffraction pattern comprising peaks at 8.3°, 9.2° and 12.1° ±0.2° 2¤ as measured by x-ray powder diffraction using an x-ray wavelength of 1.5406 Å.

Dependent claims should include additional XRPD peaks as well as additional characterising features such as single crystal data (if available), melting point (for instance as obtained from DSC), FTIR peaks and TGA characteristics.

In some cases, it may not be appropriate to characterise a polymorph solely by reference to XPRD peaks (for instance due to considerable overlap in the diffraction patterns of two different polymorphs). Additional characterising features such as single crystal data, melting point, FTIR peaks and TGA characteristics may be helpful in this instance, instead of or as well as XPRD peaks.

In this regard, it is possible to obtain grant of European patents directed to polymorphs defined without reference to crystallographic data, for instance instead by referring to melting temperature or FTIR peaks. As with claims containing features obtained by XRPD, it is always important to have a clear indication in the application of exactly how the characterising features of the polymorph were obtained.

A final consideration for claiming polymorphs in European patent applications would be to include "*product-by-process*" type language in the description. For instance, a polymorph could be defined as being "*obtainable by*" crystallisation from a specific solvent. Product-by-process claims are only allowable in certain circumstances and are unlikely to be the preferred manner in which to claim a polymorph. However, language of this type can be useful to have in the application as an additional or alternative way of defining the polymorph.

Novelty and inherent anticipation

A polymorph lacks novelty if there is an *enabling disclosure* of that polymorph in the prior art. An enabling disclosure is a disclosure which provides sufficient information for the skilled person to practice the technical teaching of the document.

It is not necessary for a disclosure to make explicit the characterising features set out in a claim (e.g. XRPD peaks) for the claimed polymorph to lack novelty. If a document describes a process in a manner which, when carried out by the skilled person, **inevitably** leads to the production of a particular product, then the document provides not only a disclosure of the process but also of the product which is inevitably obtained.

An example in the field of polymorphs would be a prior art document which describes the organic synthesis of a compound which concludes with isolation of the compound from a specific solvent by evaporation to obtain a solid sample of the compound. If the solid sample would inevitably contain a certain polymorph (e.g. because of the presence of the specific solvent), the prior art document constitutes an enabling disclosure of that polymorph, regardless of whether or not the solid sample is subsequently characterised in any way.

This means that known processes which do not explicitly refer to the production of a polymorph may nevertheless be prejudicial to the novelty of a claimed polymorph. Critically, the burden of proof is on the applicant to show that a process in the prior art would not inevitably lead to the claimed polymorph. In practice, this typically requires repeating the process described in the prior art and showing that it does not generate the claimed polymorph.

If the applicant has the advantage of being aware of potential inherent disclosures of a claimed polymorph when drafting a patent application, evidence that the claimed polymorph does not inevitably result should be included in the application as filed if possible. However, if the prior art process is only identified during subsequent prosecution, then an experimental report can be filed which shows that the claimed polymorph is not inevitably produced. The EPO will take into account the experimental results in this scenario, despite the data having been generated after the filing date of the patent application.

Inventive step

One challenge with prosecution of applications directed to a specific polymorph can be establishing inventive step. Screens of polymorphs of pharmaceutical compounds are routinely carried out during drug development. On this basis, it is often argued during prosecution that the finding of a specific preferred polymorph would have been obvious to the skilled person. However, it must be remembered that the same test for inventive step – the problem-solution approach – is used by the EPO, regardless of the subject matter claimed.

The problem-solution approach has three stages:

i. determining the "*closest prior art*";

ii. establishing the "*objective technical problem*" to be solved; and

iii. considering whether or not the claimed invention, starting

from the closest prior art and the objective technical problem, would have been obvious to the skilled person.

The closest prior art will typically be a disclosure of either an amorphous form of the known compound or a different polymorph of the known compound. The difference between the invention and the closest prior art will be a difference in crystalline form.

Formulation of the objection technical problem is generally determinative for the assessment of inventive step for polymorphs. The objective technical problem is derived from the technical effect of changing from the closest prior art (amorphous or a known polymorph) to the new claimed polymorph.

In the absence of a technical effect, the technical problem will be formulated as provision of an alternative crystalline form of the compound. In almost all cases[1], the provision of a mere alternative polymorph will be found to be obvious, given the routine nature of polymorph screening, and the polymorph will be rejected for lack of inventive step (as confirmed by the Boards of Appeal of the EPO in T 777/08[2]).

The demonstration of a particular technical effect for the claimed polymorph is therefore usually critical for securing grant of a patent. If it can be shown that the claimed polymorph has an unexpected technical advantage not observed for different solid forms of the same compound, then inventive step will generally be acknowledged.

However, it has also been established by the leading Board of Appeal decision on polymorph inventions (T 777/08) that an advantage for a polymorph compared to the amorphous form is, on its own, unlikely to be inventive if the advantages are of a type which are expected to arise. In particular, in T 777/08, it was found that, starting from the amorphous form, an improvement in filterability and drying characteristics for the polymorphic form would be obvious because crystalline polymorphs were known generally to have improved filterability and drying characteristics compared with amorphous forms. Consequently, the Board of Appeal concluded that "*[t]he arbitrary selection of a specific polymorph from a group of equally suitable candidates cannot be viewed as involving an inventive step*"[3].

The reasoning in T 777/08 does not apply to all inventions relating to new polymorphs, for instance in situations where it has been found that, among a number of different available polymorphs, one polymorph has an unexpected advantage. In those cases, patent protection for a new polymorph of a known compound can generally be obtained before the EPO.

In particular, if the closest prior art is an amorphous form of a known compound and the application contains results comparing several different polymorphs, an improved property for one of the several polymorphs can still represent an unexpected technical effect on which inventive step can be based. Examples of properties which could form the basis of a technical effect include increased stability, improved solubility, a higher dissolution rate, reduced hygroscopicity, increased bioavailability and improved suitability for formulation in a particular manner (for instance as a dry powder for inhalation). If it is shown that this advantage is only observed for one polymorph amongst several different polymorphs and that this could not have been predicted in advance, then the polymorph is likely to be found to provide a non-obvious solution to the objective technical problem, and will thus enjoy an inventive step at the European patent office.

It should also be noted that the finding of lack of inventive step in T 777/08 relates to reliance on an advantage which would have already been expected by the skilled person. A later decision of the Board of Appeal (T 1422/12) has found that even if there is only a single polymorph identified, an advantage observed for that polymorph compared with the amorphous form can lead in an inventive step, provided that the advantage itself would not have been anticipated by the skilled person.

More specifically, T 1422/12 concerned an application which related to a specific polymorph of tigecycline characterised by reference to various peaks in its XRPD pattern. The application was refused during examination for lack of inventive step over the amorphous form of tigecycline. Comparative data had been filed during examination showing that the claimed polymorph of tigecycline was more stable than amorphous tigecycline *with respect to epimerisation*, but this was not accepted by the examining division. The Board of Appeal found that, starting from the amorphous form, it would not have been obvious to the skilled person that formation of a polymorph of tigecycline would overcome the known issue of epimerisation and the decision of the examining division was overturned. This case demonstrates that by re-formulating the technical problem to be solved (i.e. "*the provision of a solid form more stable with respect to epimerisation*" rather than "*the provision of a more stable solid form*") inventive step may be demonstrated, even without providing data comparing the claimed polymorph with other polymorphs.

Comparative data will usually be necessary to demonstrate any advantage relied on for inventive step. While it is preferable that any experimental results are included in the application as filed, the European Patent Office is often willing to accept data filed at a later date in support of inventive step[4].

Best practice when drafting new polymorph patent applications

Bearing in mind the above discussion, the following points should be considered when drafting a European patent application for a new polymorph.

- A clear narrative should be presented for inventive step from the outset. The more specific the advantage of the polymorph of the invention, the more compelling arguments for inventive step are likely to be to a European examiner.
- A polymorph which is shown to have an advantage compared with ten different polymorphs of a known compound is probably more likely to be found to be inventive than a polymorph which has only been compared with one other polymorph (or no other polymorphs). If comparative data is only provided with respect to the amorphous form, it may be difficult to demonstrate inventive step unless a very specific technical effect is observed.
- Comparative data should ideally be included in the application as filed. It can, however, usually be filed at a later stage before the EPO if necessary.
- So far as possible, all known forms of the compound (including the amorphous form and any known polymorphs) should be acknowledged in the application. Given that any disclosed process for producing a solid form of the compound could represent an inherent anticipation of a polymorph of the compound, it would ideally be clarified in the application as filed what forms would result from the prior art processes.

Although the above points are focussed particularly on European Patent Office practice, in our experience most other patent offices (other than those, such as the Indian Patent Office, which impose additional requirements for polymorphs to be patentable) examine polymorph patent applications in a similar manner. Accordingly, these practice points can provide the basis of a global patent strategy for a new polymorph.

Conclusion

Polymorphs can in principle be treated as any other invention before the EPO. While decisions such as T 777/08 have established that the mere provision of a polymorph does not constitute a patentable invention, this decision does not preclude applicants from obtaining grant of patents for a polymorphs. It is entirely possible to secure grant of a useful patent for a new polymorph of a known compound provided that (i) the polymorph is appropriately claimed and (ii) a credible narrative for inventive step is presented which is based on comparative data showing an unexpected advantage for the specific polymorph claimed.

Footnotes

1. Possible exceptions might be where it is shown that it was very difficult to make the polymorph or there was a strong prejudice in the prior art against carrying out the process leading to production of the polymorph (for instance due to use of a highly unusual solvent), but such arguments would be hard to successfully advance.
2. Headnote 1 of T 777/08: "*the mere provision of a crystalline form of a known pharmaceutically active compound cannot be regarded as involving an inventive step*".
3. Headnote 2 of T 777/08.
4. There is a complex body of case law relating to the admissibility of post-filed evidence to establish inventive step, governing (a) the level of data needed in the application as filed for a plausible disclosure of biological efficacy and (b) the extent to which any new advantage referenced for inventive step must be foreshadowed in the application as filed.

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