Pharmaceutical Polymorphs and Patentability

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Introduction

Patents in the pharmaceutical industry are simultaneously critically important and controversial. While controversial because of their role in allowing pharmaceutical companies to maintain exclusivity on a pharmaceutical product, the lifesaving treatments and public health benefits that arise therefrom cannot be denied. One important aspect in the life of a drug is the possible development and marketing of a polymorphic crystal of the active chemical entity. Patents on polymorphic forms of an already marketed drug (or clinical candidate) can extend patent protection past the expiration of the original patent to a drug composition of matter. It is important to consider the nature of possible rejections that can arise when drafting an application for a polymorph because otherwise it might be impossible to overcome once a rejection arrives. The purpose of this article is to introduce the chemical and pharmaceutical patent attorney to drug polymorphs, describe their importance, and help the patent attorney overcome the frequent anticipation (§ 102) and obviousness (§ 103) rejections that occur during prosecution.

What Is a Polymorph?

Polymorphism is the ability of a crystalline material (e.g. a drug molecule) to exist in more than one solid or crystal form. This may be caused by a different arrangement of the atoms in a crystal, the incorporation of a solvent molecule (e.g. water), the formation of a salt, or conformational changes within a molecule. Solvates and hydrates are separate classes of crystalline molecules, however many of the issues that are relevant for polymorphs apply here as well. Polymorphs may have different properties than an amorphous or other crystal form which, in turn, may affect important biological and physiological properties such as solubility, dissolution rate, and bioavailability. There are several methods that are used to identify and characterize crystal polymorphs; the most common methods being single crystal X-ray powder diffraction (XRPD) and Fourier transform infra-red (FTIR) spectroscopy.
strated differences in the properties or characterization of a polymorphic form compared to a different polymorphic or amorphous form can serve as the basis for patentability. While crystal polymorphism may occur in many different types of chemical entities, including inorganic molecules, polymers, and metals, the focus of this article is on small-molecule pharmaceuticals in Technology Center 1600 at the US Patent and Trademark Office.

**Why Do Polymorphs Matter?**

The typical life cycle of patents for a drug will include multiple patents beginning with the composition of matter which is often disclosed in a large genus disclosing thousands (if not more) of small molecules. Formulation and/or method of use applications will eventually be filed along with possible second medical use applications. A polymorph may be discovered at any time during the development process, including after FDA approval.

In the United States, the Food and Drug Administration (FDA) regulates protocols and establishes applications for the marketing and sales of pharmaceutical compositions. For both new drug substances and abbreviated applications for generic drug products based on said drug substance, there are specific rules with which an applicant must comply with regards to crystal polymorphs. A company filing an abbreviated application must comply with regards to crystal polymorphs routine. It could be asserted that it would be necessary for the patent holder to look for and identify different forms of a molecule. High throughput methods have been developed to make the search for polymorphs routine. It could be asserted that it would be obvious to search for and claim any polymorphs discovered. On the other hand, the fact that two molecules with the same chemical structure have different physical and/or biological properties may be asserted that the original patent does not anticipate the polymorph.

If it isn’t anticipated, then why isn’t it obvious? The FDA has required that an applicant develop “appropriate” analytical procedures to detect and analyze polymorphic forms for over 20 years, so it would seem obvious for the patent holder to look for and identify different forms of a molecule. High throughput methods have been developed to make the search for polymorphs routine. It could be asserted that it would be obvious to search for and claim any polymorphs discovered. On the other hand, the fact that two molecules with the same chemical structure have different physical and/or biological properties is rather surprising and unexpected. This is considered objective evidence for nonobviousness.

Even if it can be shown and asserted that a polymorph has unique properties thereby conferring novelty vis-a-vis the other forms, an Examiner could assert that the properties associated with the polymorph are inherent and could reject a claim on that basis. Inherency does not require that the inventor recognize the existence of a specific result or characteristic at the time of invention, so a later discovered crystal polymorph could be asserted to be inherent in a new chemical entity. To the contrary, not all molecules have polymorphs, and not all polymorphs have different properties when compared to an amorphous form. "To establish inherency, the extrinsic evidence ‘must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that"

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**Why Isn’t a Polymorph Anticipated (§102) or Obvious (§103)?**

The answer to that question is often the classic answer that lawyers love and the layman hates – it depends. A typical claim for a crystal polymorph reads as follows:

**Claim 1.** A crystalline form of [[drug molecule]] having an X-ray powder diffraction pattern characterized by peaks at two theta angles of 10 ± 0.2, 20 ± 0.2, and 30 ± 0.2 degrees.

In a typical scenario, the previously disclosed drug molecule, mostly likely an amorphous (non-crystalline) form, was disclosed in a large genus several years before the crystalline form was discovered. The chemical formula, bond connectivity and structure of the previously disclosed drug molecule and the claimed polymorph are identical. It could be asserted that the original patent anticipates the polymorph. On the other hand, in such a scenario, the original application did not disclose a crystalline form of the drug. Because a polymorph may have different physical and/or biological properties, it may be asserted that the original patent does not anticipate the polymorph.

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12 Manual of Patent Examining Procedure § 716.01(a) et seq.

13 MPEP § 2145 citing In re Dillon, 919 F.2d 688, 692, 16 USPQ2d 1897, 1901 (Fed. Cir. 1990).
it would be so recognized by persons of ordinary skill. . .Inherency, however, may not be established by probabilities or possibilities.”14 When the discovery of a polymorph takes substantial experimentation while attempting to discover something that may or may not exist and may or may not have identical biological properties and may or may not have unusual or unique conditions for its formation, it is hard to assert that a it would be recognized by a person of ordinary skill in the art. Current case law supports a rebuttal for inherent anticipation by illustrating the properties of the polymorph not possessed by the prior art.14

How to Overcome the Potential Rejections?

While the facts of every rejection will be different, a study of previous Board15 and court decisions is instructive in providing guidance to overcome the anticipation and obviousness rejections asserted against a polymorphic form.

Ex parte Ettema16 illustrates the importance of clear and specific data in the specification to convince the Board to reverse anticipation and obviousness rejections. The claims were directed to a polymorphic form of the drug aripiprazole.17 The specification and claims disclosed the XRPD data for the claimed polymorph, and the actual XRPD spectra was included in the application. The Examiner rejected the claims as anticipated and obvious over prior art polymorphic forms stating that the prior art XRPD data was identical to the claims under examination. Close examination of the data revealed two very subtle differences in the XRPD spectra that proved to be significant in the Board decision. While the spectra between the claimed polymorph and a prior art polymorph were very similar, there were two peaks (out of several dozen) that were subtly different under direct comparison. Additionally, the Applicant was able to show that the author of the prior art, assumed to be a person having ordinary skill in the art, was aware of the new claimed polymorph and suggested that these were “new, alternative crystalline structures.”

There are several important takeaways from Ex Parte Ettema. First, it is important to understand the technology in the application. Without a clear understanding that the subtle difference in the two XRPD patterns is significant, the patent attorney would not know to present arguments regarding that fact. Collecting as much data as possible about the new polymorph and including it in the specification of the application provides more material to use when responding to a rejection. In this case, additional data specifically addressing differences in formulating the claimed polymorph and the prior art was available. Without good data included in the specification, especially the actual XRPD spectra, it would have been very difficult to show specific differences between the claimed polymorph and the prior art.

Also, the authors of the prior art are probably considered to be, at the very minimum, persons having ordinary skill in the art. Their opinion, if available, regarding the relationship between the claimed invention and the prior art can have important evidentiary value with the Board. It was significant here that the applicant was able to show that the authors of the prior art were aware of the new polymorph and did not think it was equivalent to their own polymorphic forms.

In Ex Parte Gala18 claims directed to a crystal polymorph of loratadine19 were rejected as obvious over prior art disclosing the drug loratadine in combination with other anti-histaminic agents. “A pharmaceutically acceptable salt, hydrate or polymorph thereof.” The Examiner asserted obviousness and took the position that “merely changing the form, purity or another characteristic of an old product, the utility remaining the same as that for the old product, does not render the claimed product patentable.”20 The Board reversed stating that “it appears that the above-quoted language [in the prior art] constitutes boilerplate . . . without specifically suggesting that loratadine is capable of existing in the form of distinct crystalline polymorphs.” The Board also wrote: “we invite attention to In re Cofer, 354 F.2d 664, 667, 148 USPQ 268, 271 (CCPA 1966), where the court substantially discredited PTO reliance on the above-quoted proposition of law in Hartop.”

There are several important takeaways from Ex Parte Gala. First, using “boilerplate” language to encompass polymorphs, prodrugs, salts, hydrates and other forms of a small molecule may not provide the coverage desired. If the Board rejects language in the prior art as anticipating, it would be logical to conclude that such language does not disclose those forms. Second, it is important to understand any prior case law cited by the Examiner. The law is constantly changing, and the MPEP and Examiners may not have caught up with subtle and important developments. An application comprising a polymorph should contain data clearly establishing the existence of polymorphs and emphasize any differences and unexpected results as compared to the prior art. If this data is missing in the prior art, it can be more readily argued that the polymorph is not disclosed despite language suggesting otherwise.21

In Ex Parte Pfengle22 claims directed to an anhydrous polymorph of tiotropium bromide23 were rejected as anticipated and obvious. The prior art disclosed tiotropium bromide recrystallized from anhydrous solvents which the Examiner asserted would inherently generate an anhydrous crystal. The Examiner also asserted that the prior art taught that XRPD is not always determinative. Differences in sample preparation can mistakenly give identical polymorphs different XRPD patterns. The Board reversed the rejection based on the totality of the evidence. A Declaration by the inventors stated that a direct comparison was done between the

15 The Board herein refers to either the Board of Patent Appeals and Interferences (BPAI) or its successor, the Patent Trial and Appeal Board (PTAB).
17 Currently marketed by Bristol-Myers Squibb and Otsuka America and sold under the tradename of Ability®.
18 Board Appeal 2001-0987 for application 09/169,109 (non-precedential opinion).
19 Currently marketed by Schering-Plough and sold under the trade name of Claritin®.
20 Ex parte Hartop, 139 USPQ 525, 527 (Bd. Pat. App. 1962).
21 See Ex parte Cai in footnote 24 below in contrast.
22 Board Appeal 2010-004685 for application 10/976,624.
23 Currently marketed by Boehringer-Ingelheim and Pfizer under the tradename of Spiriva®.
prior art crystals prepared exactly according to the procedure in the prior art and the claimed polymorph. The XRPD, dynamic vapor sorption (DVS) data and solid state $^{13}$C NMR (Nuclear Magnetic Resonance) all gave different results.

There are a couple of important takeaways from Ex Parte Pfrengle. The usefulness of a Declaration by the inventors cannot be underestimated. More importantly however, the Declaration was written to specifically address the exact issues in the rejection, and it was explicitly clear in doing it. The Board wrote that this was a close case, so the fact that the Declaration did not rely on only one method that the Examiner suggested could be misleading (the XRPD data) and addressed the exact issue in the rejection helped to tip the balance in favor of reversal.

In Ex Parte Cai, claims to a polymorph were rejected for lack of enablement under In re Wands in conjunction with the definition of the word "compound." The specification defined "compound" to include "pharmaceutically acceptable salts, solvates, hydrates, polymorphs, enantiomers, diastereoisomers, racemates and the like of the compounds having a formula as set forth herein." The Examiner took the position that "the specification, while being enabling for a compound of [structural type I] or a pharmaceutically acceptable salt thereof, does not reasonably provide enablement for . . . polymorph thereof." The Examiners acknowledged a lack of enablement based upon the unpredictable nature of polymorphs and suggested that the discovery of working examples of polymorphs would require one skilled in the art to embark upon an extensive research program well beyond the bounds of routine experimentation.

There are several important takeaways in the Board reversal. First, the Board refers to the same prior art as the Examiner but notes that it was in reference to the development of a pharmaceutical product for commercial marketing, not simply the discovery of polymorphic crystalline forms. The standard for the development of a pharmaceutical product is not the same as for the issuance of a patent, and the application of the standard of one to the other is erroneous. An understanding of the work of the prior art is in extremely fine detail for exactly what it discloses is critical when arguing that it is not obvious. The Examiner had established both anticipation and prima facie obviousness, thereby shifting the burden of proof to the Applicant. Unlike Ex parte Pfrengle, no new evidence was provided to the Board comparing the claimed molecule with the prior art.

There is one important takeaway from Ex parte Reddy. When addressing an anticipation or obviousness rejection, always assume the Examiner has met the requirement to shift the burden of proof. It is impossible to predict if the Board will agree that anticipation and/or prima facie obviousness has been established. Without additional data to refute the rejection when the burden of proof shifted, the Applicant was only left with an argument that had been twice refuted.

Ranitidine hydrochloride is possibly the first example where polymorphism in a drug was extensively litigated. The litigation by Glaxo Inc. resulted in several decisions that are very instructive for polymorphs. One of the most important takeaways from these decisions came when Novopharm Limited filed its second ANDA to market one polymorph of ranitidine hydrochloride (identified as Form 1 and no longer under patent protection) while Glaxo Inc. marketed another (identified as Form 2 and under patent protection for approximately six more years). Form 2 of the polymorph was claimed with 32 specific peaks in the XRPD spectra and 29 specific peaks in the FTIR spectra. Glaxo argued that the presence of one peak in Novopharm’s product that was unique to the Form 2 polymorph was sufficient to prove infringement and prevent for them. It is noted that these appeals are separated by 10 years and illustrates how what was once considered undue experimentation can become routine. The patent practitioner must stay abreast of technology in the same manner as he or she stays abreast of the law because both are continuously evolving.

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25 In re Wands, 858 F.2d 731, 737, 8 USPq2d 1400, 1404 (Fed. Cir. 1988); MPEP § 2164.01.
26 Examiner’s Answer to Appeal 2001-005302 for Application 11/852,433 pg. 12.
29 This seems difficult to resolve when compared to Ex Parte Gala (ref. 18 supra) which suggests that standard language encompassing polymorphs may not provide coverage.
30 Ex parte Reddy, where the Board affirmed anticipation and obviousness rejections of a crystalline polymorph of (S)-repaglinide, is a clear contrast to Ex parte Pfrengle. The applicant argued in a product-by-process claim that the claimed polymorph was different than the prior art even though the XRPD spectra were “the same and within the margins of error of each other.” The applicant argued, without presenting any additional evidence, that the rejection was unsupported based upon a small difference in melting point between the prior art and the claimed molecule. Because patentability in a product-by-process claim is determined by the product itself, the Board determined that the Examiner had established both anticipation and prima facie obviousness, thereby shifting the burden of proof to the Applicant.
31 Previously marketed by Glaxo, Inc. and sold under the trade name Zantac; currently marketed by Boehringer Ingelheim Pharmaceuticals, Inc.
32 MPEP § 2113(II).
33 MPEP § 2112(V).
34 Board Appeal 2009-001215 for application 10/647,449.
35 The case history and multiple decisions that arose therefrom provide an excellent lesson to consider when drafting, prosecuting and litigating a patent application for a polymorph.
37 US 4,521,431, claim 2 (XRPD) and claim 1 (FTIR).
FDA approval of the ANDA. The court held, citing *Ze- nith v. Bristol-Myers Squibb*,⁴⁰ that for infringement to occur all 32 peaks in the XRPD spectra must be present in the accused product:

Clearly, the Court cannot entertain Glaxo’s argument that sightings by its experts of one or two small “peaks” in Novopharm’s ANDA indicate the presence of Form 2, a substance claimed in the ... patents by no less than twenty-nine main infra-red peaks and thirty-two main x-ray d-spacings. As a matter of law, an area ratio test dependent on the presence of a single claimed infra-red peak out of twenty-nine such peaks claimed in the patent is insufficient to prove infringement.³⁸

Glaxo was estopped from relying on a single peak area ratio test because the claims, the prosecution history and the previous litigation required that the Form 2 polymorph be different from Form 1 based on all of the peaks in the XRPD and FTIR spectra, not just one.

These cases all illustrate the thought and care that must be given during claim drafting for a polymorph. If the claims are too exacting, the patent may be so specific that it becomes almost impossible to prove infringement. On the other hand, if the claims are not specific enough, it is possible that the application will not be allowed. There is a fine line that must be considered when drafting the claims for a polymorph. Additionally, the prosecution history and any admissions made therein will provide material that can (and will) be used during either litigation or an inter partes review (IPR).

**Conclusion**

Pharmaceutical polymorphs provide an excellent way to extend the patent protection of a small molecule drug in order to recoup the billions of dollars of research and development costs incurred in bringing the drug to market. This allows for additional research and the development of new and improved products that are a key component in improving public health. It is critically important that careful thought be given to the drafting of the application and the claims therein to ensure that proper protection is possible and that the necessary supporting data is available to support prosecution. Even before the application is submitted, careful thought must be given to the possible rejections that may occur and the data needed to overcome them. By working with the inventors before, during and after submission of the application, the patent attorney will be able to ensure that the data is either included in the application or available during prosecution to greatly increase the chance of getting the application allowed and protecting the polymorph during litigation.