Looking into the Crystal Ball – Protecting Polymorphs to Lengthen the Drug Patent Life Cycle

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Innovative pharmaceutical companies are increasingly attempting to patent improved forms of their original drug compound. Crystalline forms of a drug, called polymorphs, are one such improvement.[1] A polymorph drug may provide benefits such as better efficacy, solubility, shelf life, or ease of manufacture, which can translate into increased adoption of the drug and higher sales. Patenting a polymorph also starts an additional 20-year patent term, which may help keep generic competition off the market longer.

Patentability of Polymorphs

Polymorphs are patentable subject matter in Canada and the U.S. The Federal Court of Canada dealt with the patentability of novel crystalline forms of known compounds in *Abbott Laboratories v Canada*.[2] In this case, Ratiopharm sought approval to market Clarithromycin (6-*O*-methylerythromycin) in Canada. Although Abbott did not invent the Clarithromycin compound *per se*, they did own Canadian Patent No. 2,258,606, which claimed two different crystalline versions of the polymorphic drug. The claims covered two different crystalline forms of Clarithromycin that were distinguishable by their X-ray powder diffraction (XRPD) pattern: this effectively made the crystalline forms of the compound the patented invention. As a result, Canadian Patent No. 2,258,606 is a valid patent. Its American counterpart was also granted with claims by reference to the XRPD pattern.[3]

Although polymorphs are patentable in both Canada and the U.S., the patent strategy needs to precisely align with the properties of the claimed polymorph. For example, Abbott had originally patented the polymorph “or a pharmaceutically acceptable salt thereof”. The salt of a polymorph would have a different XRPD pattern than the polymorph itself, so Abbott filed a disclaimer to delete the salt in order to make the claim accurately align with the claimed XRPD pattern.

Other cases have also upheld the patentability of a crystal form of a known compound. In *Pfizer Canada Inc v Canada*, the Federal Court had no difficulty in accepting that Canadian Patent No. 2,220,018 claims and protects specific and novel crystalline forms of atorvastatin calcium.[4] The claims themselves identified the crystalline forms based on either their XRPD pattern or their solid-state carbon-13 nuclear magnetic resonance (^{13}C NMR) pattern. This was important as the party asserting non-infringement showed only that their compounds did not share the same XRPD pattern—they failed to show that their product did not share the same ^{13}C NMR pattern. As such, the generic product could still infringe the ^{13}C NMR-based claims.

It is also important to carefully assess the prior art when deciding whether to patent a crystal. The Federal Court of Appeal has held that if prior art discloses a method that would lead to the claimed version of the compound (even if the claimed version of the compound was *not* explicitly disclosed in the prior art), then the crystal cannot be patented.[5]

Conclusion

As it stands, previously undiscovered crystals of known compounds are patentable in Canada and the U.S., but patenting crystals requires particular attention to detail when drafting a patent application: this includes disclosing the process in the application sufficiently to be reproduced by one skilled in the art, as well as establishing the non-obvious and novel nature of the claimed crystal by reference to physical properties and functional benefits. Diligence must be exercised when claiming the polymorph to ensure that the claimed form does not also cover a form that was made, even a transient form, in the prior art as this may invalidate a patent years after its issuance. So long as care is taken when researching and drafting the patent, a polymorph patent can offer an inventor useful additional protection.

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1 Polymorphism is the ability for a solid material to exist in more than one crystal form. This means that two different polymorphs with the same chemical formula may have very different properties based on their crystal structures. An example of a polymorph is $(SiO_2)_n$: this compound can crystallize into quartz or silica gel.

2 *Abbott Laboratories v Canada (Minister of Health)*, 2005 FC 1093, aff'd 2006 FCA 187, leave to appeal to SCC refused, [2006] SCCA No 292.

3 "Crystal Form II of Clarithromycin", Can Patent No 2258606, PCT Patent No PCT/US1997/013128 (25 July 1997); "Crystal Form I of Clarithromycin", US Patent No 5858986 (29 July 1996). However, the corresponding European patent (EP0915898) was revoked after being granted for the unrelated reason that the subject matter in the claims extended beyond the content of the application filed: T 1772/06 at 1, European Patent Bulletin 2006/06 at 555.

4 *Pfizer Canada Inc v Canada (Minister of Health)*, 2007 FC 898; "Crystalline [R-(R*,R*)]-2-(4-Fluorophenyl)-Beta,Delta-Dihydroxy-5-(1-Methylethyl)-3-Phenyl-4-[(Phenylamino)Carbonyl]-1H-Pyrrole-1-Heptanoic Acid Hemi Calcium Salt (Atorvastatin)", Can Patent No 2220018, PCT Patent No PCT/US1996/011368 (8 July 1996).

5 *Abbott Laboratories v Canada (Health)*, 2007 FCA 153 at paras 19-22, 59 CPR (4th) 30, aff'g 2005 FC 1332, 45 CPR (4th) 81.

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