Form I: Crystal Form Patents in the Federal Court of Canada – A Review of Case Law on Claims Construction and Selection Patents

June 28, 2022

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Since at least as early as the mid-1990s, a body of case law has developed in the Federal Court largely recognizing inventive ingenuity in the discovery of new crystal forms of previously known compounds. These advances relate to the scientific phenomenon of polymorphism, which occurs when a chemical compound crystalizes with different intermolecular arrangements at the molecular level. "Polymorphs", although having identical chemical structures, can have very different physical properties, impacting their usefulness as pharmaceuticals, herbicides and other specialty chemical products. As such, screening for polymorphs has long been a routine practice for innovators in these fields.

Over the past 20 years, the Federal Court and Federal Court of Appeal have decided several cases addressing the validity and infringement of patents covering polymorphs, illustrating the application of patent law principles in this important area of technology. In this "Form I" paper we present and discuss this jurisprudence as it relates to unique considerations raised by crystal form inventions on the issue of claims construction and the characterization of crystal form patents as selection patents. In our upcoming "Form II" paper we turn to validity and focus on the issues of anticipation and obviousness. As discussed below, interpreting claims to polymorphs has required the courts to tackle interesting considerations related to the stability of some crystal forms, to the use of spectral data to define the scope of monopoly and to whether the claimed crystalline form is of a kind that renders the patent a selection patent.[1]

Stability of crystal forms

The unstable nature of some forms of polymorphic compounds has raised issues in determining the appropriate claim scope related to *de minimis* quantities of claimed forms and to the temporary presence of disappearing intermediates.

In *GlaxoSmithKline Inc. et al. v. Genpharm Inc. et al.*, a *de minimis* issue was before the Federal Court in litigation relating to the anti-depressant marketed as PAXIL. The claim at issue was for a composition of matter described as "crystalline paroxetine hydrochloride hemihydrate".[2] In crystalline form, the compound existed in both hydrated and anhydrous forms, with the claimed hemihydrate being dominant over the less stable anhydrous form.[3]

The respondent Genpharm's alleged the infringing formulations were intended to contain only the anhydrous form. However, there was evidence of very small quantities of the more stable hemihydrate in some formulations, possibly resulting from "seeding" of the environment with the more stable form.[4] The court had to consider whether the claim covered any amount of the claimed substance "found anywhere, in any quantity, for any reason"[5]

Justice Heneghan decided it did not. She held that it was not sensible to interpret the claim as covering minuscule and minute amounts of the hemihydrate form which, according to the expert evidence, was extremely widespread since the discovery of the product in 1984 due to prevalent use of the drug and the factors of seeding and conversion. The court concluded the claim was limited to the hemihydrate form when it is found in a drug in sufficient quantity to meet the stated

purpose of improving the handling properties of such drug during manufacture.[6]

Building to some extent on the *de minimis* issue raised in *Paroxetine*, in *Abbott Laboratories et al. v. Minister of Health et* al., the Federal Court of Appeal had occasion to consider the applicability of claims directed to an unstable intermediate created during production of the antibiotic clarithromycin.[7] There were three patents in issue. The first, the 274 Patent, claimed a newly discovered and highly unstable Form 0 of the compound. Form 0 was inevitably produced in the process of making the previously known Form II contained in the respondent Ratiopharm's product. However, Form 0 was so unstable that it would quickly convert to another form (including Form II) and went unrecognized until it was stabilized by the inventors.[8] Nonetheless, the claim was held to cover the intermediate made by the respondent in making their Form II product. As a result, there would have been infringement despite the brief and transitory existence of Form 0, except that Form 0 (although unknown) was also inherently produced in the prior art process of making Form II. As a result, the court concluded that the respondent's allegation of invalidity due to anticipation was justified.[9]

Characterization of crystal forms

The use of spectral data to define and claim different crystal forms of a compound has also been considered in connection with construction issues. Several techniques are available to measure spectral characteristics, although the case law seems to recognize X-ray powder diffraction ("XRPD") as the most accurate and has largely validated recitation of the corresponding "2θ values" as sufficient to claim a crystal form.

For example, the Federal Court of Appeal considered claims reciting XRPD data in the 606 Patent also at issue in *Clarithromycin*. The claim specified "6-0-methylerythromycin A Form II" as characterized by peaks in the XRPD pattern and having certain 2θ values (which described the peaks).[10] In an effort to avoid the prior art, the patentee argued that by referring to "Form II", the claim imported two additional analytical measurements on Form II from the disclosure that were required to satisfy the claim (and would exclude the solvated form found in the prior art). Justice Sharlow disagreed. She held that absent a satisfactory answer as to why the results from the other two tests were not claimed, the claim would be assessed based on the scope established by the XRPD 2θ values alone. In other words, the use of XRPD data was sufficient to adequately delineate the scope of the claimed monopoly.[11]

The adequacy of claim language relying on 2θ values was again an issue in *Pfizer Canada Inc et al. v. Minister of Health et al.* in litigation relating to atorvastatin calcium, the active ingredient in the anti-cholesterol drug marketed as LIPITOR.[12] Claims 1-5 of the 018 Patent described the invention as "containing" certain 2θ values from XRPD data. The respondent, Ranbaxy argued that the invention had to be defined by more than just the 2θ values and was limited to a particular form of atorvastatin with a unique and characteristic unit cell. Justice Snider rejected this construction, instead finding that the XRPD data fully characterized the claimed invention: "[I]f the material is crystalline Form I atorvastatin hydrate with the specified XRPD peaks of Claims 1, 2, 3, 4 or 5, it is the substance claimed." She further rejected an argument that separate proof beyond the 2θ values was required to establish that the claimed substance be a hydrate. Rather, in her construction, the invention was fully defined by the XRPD peaks, which she held were the essential elements of the claims.[13]

In *Bristol-Myers Squibb Canada Co. v. Mylan Pharmaceuticals ULC,* the court had to decide whether an additional limitation on purity should be read into claims reciting XRPD data.[14] Claims 1 and 2 of the patent in issue specified 2θ values to describe Form I of the anti-retroviral HIV drug efavirenz, but without specifying any level of purity. The respondent Mylan argued that the claims were directed to a highly pure Form I of efavirenz substantially free of other polymorphic forms. Mylan reasoned that a minimum level of purity of 95% had to be inferred because that level of purity was needed to see the requisite peaks and d-spacings in the XRPD data. The applicant BMS countered that the claims did not imply any purity threshold so that a product containing any detectable level of Form I efavirenz would infringe.[15]

The court agreed with BMS. Notably, other claims did include limits on purity. For claims 1 and 2, Justice Barnes reasoned that the inventors were simply informing a reader of the XRPD pattern of Form I efavirenz without ascribing any particular level of purity to the resulting product. He accepted the evidence from BMS's expert that the presence of the stated diffraction patterns for Form I efavirenz did not mean that other crystal forms or impurities could not be present, and that those readings simply indicated to a person of skill that Form I efavirenz was present and detectable in the sample.[16]

More recently, the Federal Court considered claims relying on XRPD data in *Pfizer Canada Inc. v. Apotex Inc*. The patent in issue was for the anti-depressant o-desmethyl-venlafaxine succinate ("ODV").[17] Claim 8 recited 2θ values for seven characteristic peaks of the compound but did not explicitly refer to any particular form of ODV. The applicant Pfizer sought

a narrow construction limited to the Form 1 ODV (mono) succinate disclosed in the patent. It argued a purposive construction required the whole of the patent be taken into account. The respondent Apotex submitted the claim was not limited to crystal Form I. It argued that because the compound was characterized using XRPD data in the claim, it was impermissible to look to the disclosure to characterize the claim differently.[18]

Justice Brown agreed with Pfizer. He held that Claim 8 covers a compound that exhibits an x-ray diffraction pattern having seven characteristic peaks. He referred to the facts that the only such form disclosed in the 668 Patent was the crystalline Form I ODV (mono) succinate and that the identifier XRPD referred to Form I ODV succinate. He found that there was no other "form" that could have that XRPD data and fall within the claim, concluding that this construction gives effect to the intention of the inventor and does so in the context of the patent as a whole regarding the crystalline Form I ODV succinate.[19]

In 2022, claims reciting XRPD data were also at issue in *Merck Sharp & Dohme Corp. v. Pharmascience Inc.* [20] In this patent infringement action related to the innovative medicine JANUVIA, only the validity of the 400 Patent in issue was before the court.[21] The 400 Patent claimed the dihydrogen phosphate salt of sitagliptine and its crystalline monohydrate form. [22] Notably, unlike the cases discussed above where the adequacy of XRPD data was challenged, the parties do not appear to have questioned the use of 2θ values to claim the patented crystal forms. The court assessed the issue of obviousness (in favour of the patentee) using a claims construction generally agreed to by the parties.[23]

Selection patents of crystal forms

"Selection patents" are patents that claim a subgroup of compounds from a larger previously disclosed group and that demonstrate unexpected and advantageous properties over the known larger group of compounds.[24] As such, the issue of selection patents is often ripe for consideration in relation to the discovery of new crystal forms of previously known compounds, although it has been noted that determining whether a crystal form patent is a selection patent is not a mandatory step the court must take.[25]

In *Sitagliptin*, Justice Furlanetto addressed the selection patent requirements in an effort to put the patent in issue in the appropriate context.[26] This exercise has been consistently recognized to assist the court in "understanding the nature of the beast" it is dealing with and to contextualize the patent, making it easier to compare the facts of the case with other previous fact scenarios.[27] In *Sitagliptin*, the defendant Pharmascience objected to the characterization of the 400 Patent as a selection patent. The court accepted that the 400 Patent was directed to a compound[28] (sitagliptin) encompassed within the scope of the prior art WO498 patent, which disclosed a genus of compounds including sitagliptin. WO498 also referred to other salts and crystalline forms as being within its scope but did not specifically disclose the dihydrogen phosphate salt of sitagliptin (either as a free base or hydrochloride salt). Justice Furlanetto held that the fact that there had been a selection of a particular salt and crystalline form of a particular compound from the genus of compounds, salts and crystalline forms encompassed within WO498, and that the particular salt and crystalline form were said to have advantages over sitagliptin free base and its hydrochloride salt, which were disclosed in WO498, favoured the 400 Patent being considered a selection patent.[29]

By contrast in parallel proceedings relating to ODV discussed above, in *Pfizer Canada Inc. v. Teva Canada Limited*,[30] Teva contended that the 668 Patent in issue claiming a novel crystalline Form I ODV was an invalid selection patent. It relied on the prior art US186 and WO851 patents to describe the originating class of compounds. The court, however, concluded that the patents did not disclose the crystalline form of ODV succinate claimed in the 668 Patent. Even though the prior art disclosed ODV as a free base and fumarate salt and referred to ODV succinate and other possible salts, it did not disclose the crystalline Form I ODV succinate that was the subject-matter of the asserted claims of the 668 Patent. As such, Form I ODV succinate was considered "a new composition of matter" and not a second invention selected from the class of compounds in the prior art genus patent. The court declined to find that the 668 Patent was a selection patent.[31]

Taken as a whole, the cases discussed above show that, before addressing the validity of crystal form patents, the courts will often have to grapple with claims construction issues that may bring their own challenges. The key takeaways from the cases are that: (a) *de minimis* quantities of a crystal form may be insufficient to fall within the scope of an asserted claim, whereas the brief and transitory existence of a form inherently (and even unknowingly) produced in making another form of the compound may be found to infringe or anticipate; (b) the adequacy of claim language relying solely on 2θ values to define the scope of monopoly has been largely confirmed, and additional limitations raised in the disclosure have not been read in to such claims; and (c) in some but not all circumstances crystal form patents may be properly characterized as selection patents. The case law further shows that the courts will closely scrutinize claims to different crystal forms applying

established principles of claims construction to the unique issues raised by polymorphs.

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[1] *Pfizer Canada Inc. v. Teva Canada Limited*, 2017 FC 777("*ODV Succinate*"); *Eli Lilly Canada Inc. v. Novopharm Limited*, 2009 FC 301 ("*Raloxifene*"); *Merck Sharp & Dohme Corp v. Pharmascience Inc.*, 2022 FC 417 ("*Sitagliptin*"); *Les Laboratoires Servier v. Apotex Inc.*, 2019 FC 616 ("*Erbumine*").

[2] *GlaxoSmithKline Inc et al. v. Genpharm Inc et al.* (2003), 30 CPR (4th) 360 (FCTD) ("*Paroxetine*").

[3] Strictly speaking, "polymorphs" retain the same chemical composition, and solvates or hydrates are defined as "pseudopolymorphs".

[4] Notably on the issue of infringement Genpharm argued that GSK was to blame for the presence of the hemihydrate in its product because GSK originally made the seeds available when it discovered the hemihydrate form. Genpharm argued that a finding that its product infringes when GSK themselves contributed to the ubiquity of the hemihydrate form through widespread seeding was unfair. Unfortunately, the court, however, did not decide these points. See *Paroxetine, supra,* paras 119-129 and 148.

[5] *Paroxetine, supra,* paras 8-9.

[6] *Paroxetine, supra,* paras 73-76.

[7] *Abbott Laboratories et al. v. Minister of Health et* al. (2006), 56 CPR (4^{th}) 387 (FCA) ("*Clarithromycin*").

[8] *Clarithromycin, supra,* para 6.

[9] *Clarithromycin, supra,* paras 15-16 and 24-26.

[10] *Clarithromycin, supra,* para 31.

[11] *Clarithromycin, supra,* paras 33-39.

[12] *Pfizer Canada Inc. et al v. Minister of Health et al* (2007), 61 CPR (4^{th}) 137 (FCTD) ("*Atorvastatin*")

[13] *Atorvastatin, supra,* paras 25-28. Note that similar arguments were rejected regarding the construction of claims 6-9, which defined crystalline Form I atorvastatin hydrate as characterized by certain ^{13}C NMR shifts. The specified ^{13}C NMR shifts were also found to be the essential elements of those claims.

[14] *Bristol-Myers Squibb Canada Co. v. Mylan Pharmaceuticals ULC* (2012), 107 CPR (4^{th}) 75 (FC) ("*Efavirenz*").

[15] *Efavirenz, supra,* paras 100-106.

[16] *Efavirenz, supra,* paras. 107-109.

[17] *Pfizer Canada Inc. v. Apotex Inc.* (2017), 150 CPR (4^{th}) 1 (FC) ("*Apo-Venlafaxine*"), aff'd 2019 FCA 16.

[18] *Apo-Venlafaxine, supra,* paras. 160-161.

[19] *Apo-Venlafaxine, supra,* paras. 162-163.

[20] *Sitagliptin, supra, paras.* 112-118

[21] *Sitagliptin*, *supra*, para. 4.

[22] The 400 Patent is also directed to a process for making the DHP salt of sitagliptin as a crystalline monohydrate, its formulation as a pharmaceutical composition and its use to treat diseases affected by the inhibition of DPP-4, such as type 2 diabetes: *Sitagliptin*, *supra*, at para. 12.

[23] *Sitagliptin*, *supra*, para. 112.

[24] *Apotex Inc. v. Shire LLC*, 2021 FCA 52 ("*Lisdexamfetamine*") para. 31; *Sitagliptin*, *supra*, para. 77.

[25] *Lisdexamfetamine*, *supra*, para. 32: Failure to characterize a patent one way or another is not, in and of itself, an error of law and a finding that the characteristics of a selection patent have or have not been met is no basis upon which to attack the validity of the patent.

[26] *Sitagliptin*, *supra*, paras. 65 and 80.

[27] *Sitagliptin*, *supra*, para. 80; *Lisdexamfetamine*, *supra*, para. 33.

[28] Chemical formula:
4-oxo-4-[3-(trifuoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine.

[29] *Sitagliptin*, *supra*, para. 95.

[30] *Pfizer Canada Inc. v. Teva Canada Limited*, 2017 FC 777 ("*Teva-Venlafaxine*"), paras. 288-293, aff'd 2019 FCA 15.

[31] *Teva-Venlafaxine*, *supra*, paras. 290-291.