Form II: Anticipation and Obviousness of Crystal Form Patents in the Federal Court of Canada

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By Joshua W. Spicer and Bruna D.D. Kalinoski

Many substances exist in multiple solid crystal forms. Thus “polymorphism”—the tendency of solids to crystalize in different intermolecular arrangements—is commonly encountered in the development and manufacturing process of pharmaceuticals, herbicides and other specialty chemical products. In litigation involving patents that claim particular crystal forms, the prior art often includes different forms of the compound at issue or a genus of compounds from which it was selected for further investigation. Against this backdrop, the court is often faced with the question of whether, in light of the prior art, the steps of identifying, selecting, characterizing and making a substance in a particular form can lead to a “new” compound or requires inventive ingenuity. In this paper, we discuss how the Federal Court has considered allegations of anticipation and obviousness in the context of issues raised by the nature of polymorphic compounds. This paper follows on our earlier “Form I” paper in which we reviewed the Federal Court case law addressing the issue of claims construction for crystal form patents.

Anticipation

The unstable nature of some polymorphic compounds, and corresponding tendency for conversion from less to more stable forms, have proven significant to the issue of anticipation in at least two cases. In *Abbott Laboratories et al. v. Minister of Health et* al.,[1] the Federal Court of Appeal had to consider whether a claim to a previously unknown intermediate was anticipated when the intermediate was unknowingly created during the synthesis of a more stable prior art form of the antibiotic clarithromycin. The inventors had discovered and stabilized a new Form 0 of the compound. Following this invention, although previously unknown, it was recognized that Form 0 was inherently produced during the synthesis of the prior art Forms I and II, but Form 0 was so unstable that it quickly converted to the known forms and previously went undetected. The alleged infringement was Ratiopharm's preparation of Form II during which Form 0 was inherently produced. Abbott sued on its claim to Form 0 *per se* (not to stabilized Form 0). The court applied the long-standing principle of “what would infringe if later, anticipates if earlier” and found the claim to Form 0 was anticipated despite anyone actually knowing of its existence: “Because a person who makes Form I or Form II following the teaching of the prior art inevitably would make Form 0, that person would infringe the 274 patent as surely as Ratiopharm would infringe it by making the Form II for its product, as it proposes to do, by a method that results in the creation of Form 0.”[2]

In *GlaxoSmithKline Inc. et al. v. Genpharm Inc. et al.,* the respondent Genpharm led evidence to show that crystalline paroxetine hydrochloride was made by following a prior art patent.[3] The applicant GSK’s patent in issue related to crystalline paroxetine hydrochloride hemihydrate. GSK challenged the reliability of experiments conducted by Genpharm’s expert based on the theory of disappearing polymorphs. The theory suggests that once a more stable form of a polymorph has been made, the environment becomes “seeded” with that form (even in microscopic amounts) such that it is no longer possible to isolate the less stable form because it immediately converts (disappears) to the more stable form in the seeded environment. Relying this theory, GSK argued that, prior to the discovery of the more stable hemihydrate form in 1984, following the prior art would have led to the less stable (and non-anticipatory) anhydrous form but, once the hemihydrate form was discovered, it was no longer possible to make the anhydrous form due to seeding in the environment resulting

the manufacture of the more stable form. On the evidence, the court was not convinced it would be impossible to create the anhydrous form, but still found the reliability of the experiments was put into question because the hemihydrate form had been present in Genpharm's expert's lab when he conducted the litigation experiments. The Court also noted that the experiment used paroxetine hydrochloride to "reproduce" an example which used n-methyl paroxetine hydrochloride. Thus, Genpharm's allegation of anticipation was found to not be justified.

Obviousness

Different polymorphs can have distinct properties and are routinely screened in hopes of discovering improved compounds. The preparation of polymorphs with desired features entails manipulating various conditions. Even if every step of the process is performed with the utmost skill and knowledge, polymorphs are often obtained serendipitously with unpredictable results for properties such as solubility, dissolution, bioavailability and stability. Mindful of this scientific background, the Federal Court has made clear in the past few years that there is no hard and fast rule that all polymorph screens are obvious to try or routine. Obviousness remains a factually-laden inquiry. Although polymorph screen studies are routinely performed in the development process, whether the discovery of a compound is obvious ultimately depends on the extent and amount of effort and experimentation, as well as the predictability (or lack thereof) of the outcome.

The *Paroxetine* case[4] discussed above highlights the importance that the lack of predictability in polymorphism can play in obviousness analysis. Genpharm raised allegations of obviousness in relation to a claim for crystalline paroxetine hydrochloride hemihydrate. The closest prior art disclosed paroxetine hydrochloride in solution (*i.e.* not the claimed hemihydrate form). The applicant GSK's evidence was that, at the relevant time, development of the hemihydrate would have been a completely unexpected result, the invention of a new polymorph an uncertain science with no predictability, and the preparation and identification of polymorphs complicated. It would have been impossible to predict the results of crystallization experimentation and the properties of the hemihydrate form. Given the uncertainty in the science, the court rejected the respondent's allegation of invalidity. It held there was no indication that a skilled person would have known how to create, notice or document the benefits of the hemihydrate. The fact that the discovery of the hemihydrate was serendipitous was of no consequence to the invention's ingenuity and did not disentitle the inventor to a valid patent.[5]

In *Efavirenz,*[6] the Court recognized that, even if other crystal forms of the compound claimed in the 198 Patent at issue were known, this does not necessarily mean that useful crystal forms could be created using routine techniques. The respondent Mylan contended that, to arrive at the claimed Form I of efavirenz, inducing further polymorphic transformations of efavirenz would have been self-evident to a skilled person. However, the court agreed with the applicant BMS's expert that knowledge of the existence of a single crystalline form of a given compound offers no insight on whether additional forms exist or the properties of these potential crystal forms. The level of effort required to obtain additional polymorphs was unpredictable and the results uncertain as "polymorphs discovered might not have properties which are suitable for formulation into a drug product". At the relevant time, the amount of effort required to find Form I efavirenz was not routine or non-arduous, and it was not self-evident to the skilled person that the product obtained would be useful.[7] The court concluded that the invention of the 198 Patent was not obvious.

In two companion cases involving the 668 Patent for the antidepressant desvenlafaxine, both Teva and Apotex appealed trial decisions that the patent was not obvious.[8] The patent claimed crystalline Form I ODV succinate, a new compound that had never before been made or disclosed.[9] Central to the appeals was the argument that the beneficial properties of Form I ODV succinate should not be included as part of the inventive concept. The parties agreed,[10] but the appellants argued that the trial judge had nonetheless still considered the properties of Form I ODV succinate, implying that it was necessary for the skilled person to be able to predict them from the prior art.

In dismissing the appeals, the Federal Court of Appeal held that, taken as a whole, the trial judge's decision was grounded on the fact that Form I itself was not obvious, not that the properties were not predictable.[11] The trial judge reasoned that "the number of experiments required to move from the acceptable pharmaceutical salts to the Form I ODV succinate was extremely large…and in the nature of a research program, not routine experimentation",[12], which involved inventive ingenuity. The trial judge also concluded that "while the prior art explicitly disclosed ODV as a free base and a fumarate salt, and ODV succinate as a potential salt, no crystal form of that salt let alone the crystalline Form I ODV succinate had ever been expressly disclosed, made or characterized."[13] Notably, the appellate court affirmed that no "hard and fast rules" in the jurisprudence establish that salt forms, polymorphs or crystalline forms are presumptively obvious and the assessment of whether screen studies and other experimentation are obvious will turn on the facts of each case.[14]

In *Sitagliptin*,[15] the 400 Patent at issue related to the dihydrogenphosphate ("DHP") salt of sitagliptin and its crystalline monohydrate form, and it was found to be a selection patent. In assessing obviousness, the Federal Court undertook the principled factual analysis of the invention story as in *Desvenlafaxine* and held that the work and effort required to obtain the claimed crystalline monohydrate of the sitagliptin compound was extensive and not predictable. The trial judge relied on the statement by the Federal Court of Appeal in *Desvenlafaxine* that there is no overriding principle that all screen studies are obvious and matters of routine, or that polymorph identification will always be unobvious.[16]

On the facts, the trial judge found that there was insufficient motivation to focus on the particular crystalline form of a salt of *sitagliptin* over the other compounds disclosed in the genus patent and no differentiation between the properties of the compounds in the genus patent.[17] Specifically, the genus patent referred to a class of compounds which were potent inhibitors of dipeptidyl peptidase-4, an enzyme that modulates blood sugar levels and is therefore useful for the treatment of Type 2 diabetes. The genus patent specifically disclosed sitagliptin as a free base and the hydrochloride salt, but it also generally referred to other salts and crystalline forms as being within its scope. Neither the compound nor its suitability for making medicaments would have been self-evident to explore. The court held the claims were not obvious.[18]

Advances in technology

The Federal Court jurisprudence discussed above demonstrates a consistent recognition of the inventiveness of new crystal forms. However, as recent proceedings before the Patent Appeal Board illustrate, changes may be on the horizon with advances in polymorph screening technology. In considering patentability of Form B polymorphs of azoxystobin (a broad spectrum agricultural and horticultural fungicide), the Patent Appeal Board recently had the occasion to apply the principle from *Desvenlafaxine*, namely, that no "hard and fast rules" on obviousness exist when it comes to assessing screen studies or other forms of experimentation.[19] However, to the opposite effect of the rulings in *Desvenlafaxine*, *Sitagliptin*, *Efavirenz*, and *Paroxetine*, the board found there was no ingenuity in the steps of producing, identifying and characterizing Form B polymorphs of azoxystobin obvious.

At the outset, the board noted that *Desvenlafaxine*'s finding of non-obvious concerned a relevant date of 2002 that goes back six years before the relevant date for the obviousness assessment of the patent application for Form B azoxystobin of 2008. The board noted that since 2002, the common general knowledge concerning polymorph screening had evolved significantly to include the use of automated high-throughput screening technology.[20] Consequently, the board held that the characterization of the common general knowledge in recent polymorph decisions was not relevant to the case before it.[21]

The board further noted that no comparative data of the beneficial properties of the claimed forms over other known forms of azoxystobin existed in the description.[22] Critically, the characterization of the claimed forms was limited to spectral data, and there was no suggestion that the claimed forms were advantageous compared to the forms in the prior art. Absent further characterization, the skilled person would have produced the claimed forms without difficulty in conducting routine polymorph screens to discover new crystalline forms of azoxystobin. Moreover, consistent with the description concerning the course of conduct that led to the invention, the board found there was motivation to search for forms of azoxystrobin suitable to industrial manufacture. The skilled person would have started off with routine polymorph screening, and in doing so, would have found Form B of azoxystrobin and mixtures of Form A and Form B without difficulty.[23] The board recommended that the application be refused for obviousness.

Taken as a whole, these cases show that patentees should be prepared to face forceful arguments on the basis of anticipation and obviousness, both by their adversary litigants and the examiner in the patent office. The anticipation cases discussed above show the risk of inherent anticipation and the importance of consistent and solid expert evidence on experimental litigation testing. The obviousness cases, in turn, show that patentees would do well to develop a compelling narrative of the story of the invention that shows the extent and amount of effort required to arrive at the claimed invention and pre-emptively gather evidence to support the story of the invention. There is also a developing question of whether advances in screening technology represent an emerging threat to patents with more recent claim dates.

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[1] *Abbott Laboratories et al. v. Minister of Health et* al., 2006 FCA 187 at paras. 24-26 ("*Clarithromycin*").

[2] *Clarithromycin* supra at para. 24-26.

[3] *GlaxoSmithKline Inc. et al. v. Genpharm Inc et al.*, 2003 FC 1248, (2003) 30 CPR (4th) 360 (FC) ("*Paroxetine*").

[4] *GlaxoSmithKline v. Genpharm*, 2003 FC 1248, 30 CPR (4th) 360 ("*Paroxetine*") at paras. 76.

[5] *Paroxetine* supra at para. 86.

[6] *Bristol-Myers Squibb Canada Co. v. Mylan Pharmaceuticals ULC*, 2012 FC 1142 paras. 116-121 ("*Efavirenz*").

[7] *Efavirenz* supra at paras. 119-120.

[8] *Pfizer Canada Inc. v. Teva Canada Ltd.,* 2017 FC 777 aff'd 2019 FCA 15 ("*Desvenlafaxine-Teva*") and *Pfizer Canada Inc. v. Apotex Inc.,* 2017 FC 774 aff'd 2019 FCA 16 ("*Desvenlafaxine-Apotex*"), collectively, *Desvenlafaxine*.

[9] *FC Desvenlafaxine-Teva* supra at para. 27.

[10] *FC Desvenlafaxine-Teva* supra at para. 32.

[11] *FC Desvenlafaxine-Teva* supra at para. 35; *FC Desvenlafaxine-Apotex* supra at para. 39.

[12] *FCA Desvenlafaxine-Teva* supra at para. 192; *FCA Desvenlafaxine-Apotex* supra at para. 39.

[13] Trial reasons at para. 229 quoted by FCA at para. 38.

[14] *FCA Desvenlafaxine-Teva* supra at para. 39-40; *FCA Desvenlafaxine-Apotex* supra at para. 39

[15] *Merck Sharp & Dohme Corp v. Pharmascience Inc.*, 2022 FC 417 ("*Sitagliptin*").

[16] *Sitagliptin* supra at para. 183.

[17] *Sitagliptin* supra at paras. 201-202.

[18] *Sitagliptin* supra at para. 249.

[19] *Adama Makhteshim Ltd.*, 2022 CACP 10 ("*Adama*") at para. 37.

[20] *Adama* supra at para. 38.

[21] *Adama* supra at para. 37.

[22] *Adama* supra at paras. 71 and 79.

[23] *Adama* supra at para. 88-89.