Inducing Infringement by Product Monographs & Skill and Judgment in Medical Use Claims: Key Takeaways from the Federal Court's decision in Hoffman-La Roche Limited v Sandoz Canada Inc.

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The recent Federal Court decision *Hoffmann-La Roche Limited v Sandoz Canada Inc.*[1] concerns Roche's 2,667,654 (654 patent) and 2,709,997 (997 patent) patents related to pirfenidone (ESBRIET) for the treatment of idiopathic pulmonary fibrosis (IPF). It touches on the issues of claim construction of Swiss style use claims, the issue of what amounts to inducement of infringement by a pharmaceutical manufacturer, evidentiary issues of Wayback printouts, and invalidity issues of double patenting, obviousness, and methods of medical treatment.

The 654 patent, "Method of Providing Pirfenidone Therapy to a Patient", claims a dose escalation regimen that minimizes adverse events. The 997 patent, "Pirfenidone Treatment for Patients with Atypical Liver Function", claims a therapeutically effective dose of pirfenidone for patients following pirfenidone-related abnormal liver function. Both patents were issued to InterMune, which was subsequently acquired by Roche in 2014.[2]

Sandoz is seeking approval for its own pirfenidone capsules and tablets. Roche alleged the Sandoz pirfenidone will infringe and/or induce infringement of the 654 and 997 patents. In response, Sandoz challenged the validity of the 654 and 997 patents on the basis of anticipation (654 patent), double patenting (997 patent), obviousness, unpatentable subject matter (methods of medical treatment), lack of utility, insufficiency of disclosure, overbreadth and/or ambiguity (654 patent).

Admissibility of Wayback Evidence

A law clerk for Sandoz's counsel provided evidence in support of the admissibility of a printout of ClinicalTrials.gov 2006 generated using the Wayback Machine. Justice Manson noted that the Wayback Machine is generally reliable, but Sandoz failed to establish the authenticity of the printout pursuant to s. 31.1 of the *Canada Evidence Act* and failed to meet the best evidence rule under s. 31.2 of the *Canada Evidence Act*.

Sandoz was seeking to admit a printout from ClinicalTrials.gov demonstrating an InterMune-sponsored phase III study of pirfenidone in IPF patients. The printout was being relied on to establish the prior art as of October 9, 2006, which would have been beneficial given the 654 patent priority date of December 18, 2006. The law clerk was to provide evidence as to how the information was obtained.

Justice Manson held that since the information on the printout was captured at different points in time the October 9, 2006 date could not be established. Further "it could not be established that the prior art, as contained in the printout, was publicly available at the relevant time."[3] In making this decision Justice Manson relied on *ME2 Productions, Inc v Doe*, which stated that the affidavits of law clerks do not meet the requirements of Rule 81.[4] Rather, a witness from InterMune should have testified to the issue.

This decision raises future concerns regarding the admissibility of the Wayback Machine evidence. The Federal Court in *Candrug Health Solutions Inc. v Thorkelson* affirmed the reliability of the Wayback Machine as an accurate representation of websites at the relevant time.[5] Although the affidavits of a law clerk cannot establish the authenticity of prior art, it

remains unclear as to whether the Wayback Machine may be an exception to the rule. Future cases seeking to rely on Wayback evidence will be necessary to clarify how such evidence may be admissible.

Claim Construction

Sandoz argued that Swiss-style use claims do not apply in Canada (a Swiss-style claim recites the use of an old compound in the manufacture of a medicament for the treatment of a new disorder). Rather, Sandoz argued that they should be "properly construed as use claims where the alleged invention resides in the use and not in the manufacture or composition of the medicine."[6]

Justice Manson agreed with Sandoz that the Swiss-style use claims of the 654 and 997 patents are properly construed as use claims, and not in the manufacture or composition of pirfenidone. The 654 and 997 patents cannot be said to enable a *new* use of pirfenidone as they merely disclose a dosing regimen.

Induced Infringement

Justice Manson held that there was no direct infringement of the 654 and 997 patents but found that Sandoz would induce infringement of the 654 patent.

Roche claimed that Sandoz will induce infringement by physicians, pharmacists and patients through the Sandoz product monographs, packaging and labelling. Sandoz argued that the three-part test for induced infringement was not satisfied because (1) pharmacists and physicians will not personally use pirfenidone in the treatment of IPF patients; (2) there is no evidence of direct infringement by patients due to individualized dosing; and (3) Sandoz did not possess the required influence and knowledge.

Justice Manson held that the dosage regimen in the 654 patent is the default treatment, and thus the same regimen will continue to be prescribed for the generic pirfenidone product, thereby infringing the claims. Further, the product monographs provide clear directions which would result in infringement of the dose escalation regimen. Justice Manson accepted Roche's evidence that some physicians will consult the Sandoz product monographs. This is due to the rarity of IPF, such that not all prescribing physicians possess the specialized pirfenidone dosing knowledge. The fact that at least some prescribing physicians would consult the product monographs was considered sufficient to establish infringement.

This approach differs from that taken in earlier decisions. In *Abbott Laboratories Limited v Canada (Ministry of National Health and Welfare)*, it was admitted that physicians rarely look at a product monograph when making a prescription. Nonetheless, the product monograph was still held to induce infringement.[7] Further, in *Novopharm Limited v Sanofi-Aventis Canada Inc.*, Justice Sharlow noted that infringement by inducement may be established by inferences reasonably drawn from a product monograph.[8] More recently, in *Hospira Healthcare Corporation v Kennedy Trust for Rheumatology Research*, Hospira's product monograph was held to amount to a clear instruction for infringement thus amounting to strong evidence of influence.[9] These decisions have focused on the content of the product monograph without seemingly giving weight to the prescribing practices of physicians.

Invalidity

Double Patenting

The 997 patent was held to be invalid on the basis that it is not patentably distinct from the earlier 2,631,646 (646) patent, which disclosed the use of pirfenidone in the manufacture of a medicament, three times a day, for the treatment of IPF to reduce dizziness. The 646 and 997 patents both teach the same daily dose, three times a day with food. The fact that the 997 patent teaches rechallenging pirfenidone following abnormal liver biomarkers was not sufficient to overcome the obviousness-type double patenting issue. Given that the POSITA would know pirfenidone is metabolized by the liver, the classification system for liver biomarkers and strategies for managing the associated adverse events, the rechallenging of an IPF patient with pirfenidone following the liver biomarker abnormality was considered to be obvious. Thus, Justice Manson held that the 997 lacks an inventive step over the earlier 646 patent.

Obviousness

The 654 patent teaches a dosing regimen to decrease the adverse effects and improve the tolerability of pirfenidone. The issue rests on whether the dosage escalation regimen itself would be obvious to the POSITA at the relevant date. The prior art had disclosed the oral administration, three times a day, administration with food and reduction in photosensitivity. The

common general knowledge provided more frequent dosing with a gradual escalation period to the target dose, including the increase in thirds of the target dose. Further, the maximum dose of 2400 mg/day, extrapolated based on a 60kg patient, was within the skill and knowledge of the POSITA. Given the state of the prior art, Justice Manson held that the dosage regimen taught by the 654 patent was obvious to try. In coming to the obvious to try conclusion, he held that prolonged or arduous experimentation would not have been required to arrive at the 654 dosage regimen. Moreover, the actual effort exerted by the inventor was immaterial in this determination. Finally, at the relevant time, pirfenidone was a promising investigational drug for the treatment of IPF, thus providing the motivation for the patent.

The 997 patent teaches that a patient who has experienced a grade 2 liver abnormality can still receive the full dose of pirfenidone. As mentioned in the context of double patenting, the POSITA possesses knowledge for management of drug-induced liver toxicity. As such, it was found that it would have been obvious to rechallenge with pirfenidone.

Patentable Subject Matter

Methods of medical treatment are not patentable subject matter in Canada. Such claims that prevent or restrict physicians from applying skill and judgment are thus considered invalid. Fixed dosages or fixed dosage schedules typically are not considered to restrict professional skill or judgment, unless there is evidence to the contrary (see our article here). Such evidence to the contrary was held to exist in the 654 patent, which discloses a dose escalation regimen that is not appropriate for all patients taking pirfenidone for the treatment of IPF. The anticipated adverse effects must be monitored, and the possibility for dose adjustments may be warranted thereby requiring the exercise of skill and judgment. Similarly, the 997 patent is not appropriate for all patients and requires an assessment of the individual patient's circumstances. As such, both the 654 and 997 patents were held to be invalid as they disclose unpatentable methods of medical treatment.

The Canadian Intellectual Property Office guidance document (PN2020-04) clearly states that professional skill and judgment may be involved if a medical professional is expected to monitor or make adjustments to the treatment, or make a selection of a dosage from a claimed range (i.e., in cases where not all dosages in the range will work for all subjects within the treatment group). In the present case, the necessity of monitoring and adjusting the dosage was inferred from expert evidence. This builds upon the existing case law in *Janssen Inc v Mylan Pharmaceuticals* which similarly invalidated claims due to the requirement of monitoring for adverse reactions.[10]

Practice Points

Fixed dosage regimens and ranges, including those that require the calculation of body weight or body surface area, have been deemed not to require professional skill and judgment. This case further clarifies that where a claimed dosage will not be appropriate for all patients, professional skill and judgment are required. Applicants should keep in mind that the requirement to monitor and modify a fixed dosage regimen may not be considered patentable subject matter in Canada. It will be interesting to follow any future developments.

1 *Hoffmann-La Roche Limited v Sandoz Canada Inc.,* 2021 FC 384.
2 "Roche and InterMune reach definitive merger agreement" (24 August 2014) Online: *Roche* https://www.roche.com/media/releases/med-cor-2014-08-24.htm
3 *Hoffmann-La Roche Limited v Sandoz Canada Inc.,* 2021 FC 384 at para 52.
4 *ME2 Productions, Inc v Doe,* 2019 FC 214 at paras 120 – 122.
5 *Candrug Health Solutions Inc. v Thorkelson*, 2007 FC 411 at para 20.
6 *Hoffmann-La Roche Limited v Sandoz Canada Inc.,* 2021 FC 384 at para 96.
7 *Abbott Laboratories Limited v Canada (Ministry of National Health and Welfare),* 2006 FC 1411 at paras 40-42.
8 *Novopharm Limited v Sanofi-Aventis Canada Inc.,* 2007 FCA 167 at para 11.
9 *Hospira Healthcare Corporation v Kennedy Trust for Rheumatology Research*, 2018 FC 259 at para 331.
10 *Janssen Inc v Mylan Pharmaceuticals ULC*, 2010 FC 1123.