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Federal Court invalidates tadalafil dosage patent finding dose selection to be routine

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On August 6, 2020, the Federal Court issued its decision in *Eli Lilly Canada Inc. v. Mylan Pharmaceuticals ULC*, 2020 FC 816, invalidating Eli Lilly's patent, Canadian Patent No. 2,371,684 (the 684 Patent) directed to low doses of tadalafil, on the grounds of both anticipation and obviousness. The decision was a major victory for Osler's long-time client Mylan Pharmaceuticals ULC (Mylan) and followed a common invalidity trial across multiple proceedings involving Eli Lilly and generics Mylan, Apotex, Teva, Pharmascience and Riva. Mylan had earlier succeeded in respect of the 684 Patent in a proceeding under the *Patented Medicines (Notice of Compliance) Regulations* (*Eli Lilly Canada Inc. v. Mylan Pharmaceuticals ULC*, 2015 FC 125).

Background on Eli Lilly's dosage patent

The 684 Patent is directed to compositions containing tadalafil in doses between 1 and 20 mg to treat erectile dysfunction. The 684 Patent follows on two earlier patents, the first directed to the tadalafil compound itself and the second directed to its use to treat erectile dysfunction. Eli Lilly alleged that doses between 1 and 20 mg were surprisingly effective, with reduced side effects, particularly in light of the commercially available doses of 50 and 100 mg for the first-in-class product Viagra (sildenafil).

Following its unsuccessful PM(NOC) proceeding, Eli Lilly brought patent infringement claims against several generic entrants, seeking significant damages from all defendants. At trial, Eli Lilly alleged that the 684 Patent was a selection patent, with claimed doses having a superior side effect profile to higher doses, and it led detailed evidence of the drug development story resulting in the claimed doses. This evidence, from two companies that preceded Eli Lilly in the development of tadalafil (Glaxo and ICOS), was intended to prove that pre-clinical and early clinical evidence pointed toward higher doses and that serious safety questions emerged that militated against development of the drug generally, and of those doses in particular.

Although found to ultimately be unpersuasive, Eli Lilly's fresh evidence was sufficient to cause the trial judge to consider the matter anew and not find that Eli Lilly was estopped from re-litigating the findings of the PM(NOC) decision.

No selection patent where alleged advantages are not unique

Eli Lilly argued that the 684 Patent was a selection patent based principally on improved facial flushing experienced by patients taking lower tadalafil doses in comparison with sildenafil. The trial judge described this position as a "moving target" throughout the trial,

even until oral closing arguments.

The Court was unpersuaded by Eli Lilly's selection patent allegation because the flushing advantage was not unique to the claimed doses, as is required under the selection patent criteria set out in *In re Farbenindustrie AG's Patents* (1930), 47 RPC 289 (ChD). Even at the highest doses measured, tadalafil patients experienced reduced facial flushing, and the flushing benefit was quite clear at doses above 20 mg. Furthermore, reduced or eliminated facial flushing was not the focus of the patent or the claims and was not specifically described as being the invention in the disclosure to the 684 Patent.

Claims construed with fidelity to claims language

The Court was required to resolve one critical claim construction dispute — namely, whether the claims were construed as having a limitation of one dose per day. Eli Lilly attempted to use this claim construction argument to suffuse a side effect benefit into the claims.

The Court received expert evidence on the issue. Eli Lilly's expert was found to lack credibility because his expert report was largely identical to a report he had tendered in U.S. litigation, where, unlike for the claims in suit in Canada, the U.S. claim language specifically included a maximum daily dose. The trial judge stated that she "was not convinced [the witness] completely turned his mind to the issues and concept at play in this particular litigation" and consequently gave his opinion less weight. The Court preferred the evidence of the defendants' expert, who emphasized the language of the claims, which the Court found to be unambiguous.

Narrow dosage range anticipated by broader range

Following the claim construction from the previous PM(NOC) proceeding, the trial judge concluded that the claims were anticipated by a prior tadalafil patent directed to the use of tadalafil in the treatment of erectile dysfunction. The prior patent had disclosed a dosage range for tadalafil, broader than the range claimed in the 684 Patent. Although Eli Lilly alleged that the prior patent provided insufficient teaching on dosing and pointed to higher doses, the Court concluded that the lower doses were disclosed.

In finding that the prior patent enabled a skilled person to arrive at low doses using only routine trials, the Court favoured one of the defendants' expert witnesses who had been blinded. The witness had been provided prior art to the 684 Patent and selected early-stage tadalafil development information that she considered routine, but she had never been exposed (i.e., she was "blinded") to the 684 Patent or the commercial tadalafil doses. The trial judge found that the witness was direct, straightforward and engaging and that she came across as independent, honest and thorough. Her evidence was that dose selection is routine pharmaceutical work performed without undue burden, and that a skilled team would have no problem identifying what would be minimally effective in treating male erectile dysfunction.

Routine dose selection found to be obvious

In assessing obviousness, the Court echoed recent case law equating the identification of the inventive concept with determining the subject-matter discernible from the claims. On that basis, obviousness was assessed based on the Court's claim construction.

The Court discounted Eli Lilly's arguments that the earliest development effort by Glaxo

revealed serious safety problems with tadalafil. The Court found that these issues were addressed quite handily and that human studies continued unimpeded in Europe even if they were temporarily stalled in the United States. Eli Lilly's argument that Glaxo was focused solely on higher doses was contradicted by documents indicating that Glaxo was aware that lower doses in the 10 mg range were effective.

The Court found the claimed doses to be obvious. The skilled team attempting to dose tadalafil would start with information in prior art tadalafil patents, as well as comparative information about sildenafil. The skilled team would make a rough prediction of dose within the prior-disclosed range. Then, using all available information in the prior art, the skilled team could design a Phase II dose-ranging study, graph the dose-response curve, identify side effects and select the dose range providing the best balance between safety, efficacy and tolerability. If an initial Phase II study did not allow the drawing of the full dose-response curve, a second study could be performed. All this work involved known and routine trial design techniques.

Eli Lilly's expert witnesses accorded less weight due to inattentiveness and impartiality issues

Overall, the trial judge found the defendants' witnesses, and in particular their expert witnesses, to be more credible than Eli Lilly's witnesses.

As noted above, the trial judge accorded less weight to one of Eli Lilly's witnesses, Dr. Hartmut Derendorf, due to the fact that his report was highly similar to a U.S. expert report, despite the Canadian and U.S. patents having materially different patent claims. The trial judge noted that "[n]umerous typos and mistakes specific to the US patent wording were carried over to the Canadian report." The trial judge indicated that "[t]hese circumstances cast a shadow on Dr. Derendorf's report and opinions in regards to the 684 Patent."

A second Eli Lilly witness was singled out for having particular impartiality issues.

The defendants objected to Eli Lilly's urology expert, Dr. Gerald Brock, on the basis that he was so biased that he could not even fulfill his most basic duty to assist the Court by providing an impartial and independent expert deposition.

The trial judge noted that simply consulting and being remunerated by the pharmaceutical industry is not disqualifying. However, for Dr. Brock, the partiality problem extended further because he admitted under cross-examination to changing his opinions that he had previously given to support other Eli Lilly tadalafil patents and a Pfizer sildenafil patent. His contradictions related to areas helpful to Eli Lilly, and his explanations for his contradictory evidence were found to be unconvincing.

Concluding comments

Eli Lilly has undertaken extensive litigation around the world involving its blockbuster drug Cialis. This latest decision in the Canadian tadalafil patent saga sends a strong signal that patents directed to dose selection will be difficult to sustain. The decision continues the recent judicial trend toward emphasis on claims language in carrying out claim construction and assessing invalidity. The decision also highlights the importance of expert witnesses, including ensuring expert impartiality and determining what expert evidence will best assist the Court.

The authors of this article represented the defendant Mylan Pharmaceuticals ULC in *Eli Lilly Canada Inc. v. Mylan Pharmaceuticals ULC*, 2020 FC 816. The decision remains subject to appeal.

If you have any questions about this case or other issues, please contact J. Bradley White at bwhite@osler.com or Nathaniel Lipkus at nlipkus@osler.com.