Federal Court of Appeal | Cour d'appel fédérale

Date: 20120329

Docket: A-226-11

Citation: 2012 FCA 103

CORAM: **SHARLOW J.A.**
GAUTHIER J.A.
MAINVILLE J.A.

BETWEEN:

MYLAN PHARMACEUTICALS ULC

Appellant

and

PFIZER CANADA INC., EISAI CO., LTD AND THE MINISTER OF HEALTH

Respondents

Heard at Ottawa, Ontario, on February 22, 2012.

Judgment delivered at Ottawa, Ontario, on March 29, 2012.

REASONS FOR JUDGMENT BY: MAINVILLE J.A.

CONCURRED IN BY: SHARLOW J.A.
GAUTHIER J.A.

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REASONS FOR JUDGMENT

MAINVILLE J.A.

[1] Mylan Pharmaceuticals ULC ("Mylan") is appealing a judgment of Hughes J. of the Federal Court ("application judge") cited as 2011 FC 547 ("Reasons") that allowed the application of Pfizer Canada Inc. ("Pfizer") and Eisai Co., Ltd. ("Eisai") under the *Patented Medicines (Notice of Compliance) Regulations*, SOR/93-133 ("*NOC Regulations*") for an order prohibiting the Minister of Health from issuing a notice of compliance to Mylan for its generic version of Aricept – a drug approved in Canada for the treatment of dementia of the Alzheimer's type - until the expiry of Canadian Patent No. 1,338,808 ("'808 Patent"), which is owned by Eisai and licensed in Canada to

Pfizer. The ‘808 Patent includes a claim for a compound known as donepezil, which is the active ingredient in Aricept.

[2] Mylan is challenging the application judge’s refusal to consider its submission that inaccurate data are contained in the ‘808 Patent. That refusal was based on the application judge’s finding that no allegation had been made by Mylan in its Notice of Allegation as to whether the ‘808 Patent fully and accurately set out the work done by Eisai.

[3] Mylan also submits that the application judge erred in not finding that the ‘808 Patent promises that donepezil has acceptable toxicity and is safer and longer acting than the prior art compounds of physostigmine and tracrine, and that, consequently, the patent is invalid for failure to disclose a factual basis sufficient to soundly predict such a promise.

The regulatory process at issue

[4] In order to sell a new drug in Canada, an innovator must obtain regulatory approval from the Minister of Health under Division 8 of Part C of the *Food and Drug Regulations*, C.R.C. c. 870. This approval is by way of a notice of compliance, which may be issued only following a submission containing sufficient information and material enabling the Minister to assess the safety and effectiveness of the drug, including detailed reports of the tests made to establish its safety for the purpose and under the conditions of use recommended, and substantial evidence of its clinical effectiveness.

[5] If a generic manufacturer then wishes to market a generic version of that drug, it must file a submission (designated as an abbreviated new drug submission) with the Minister of Health in which it makes specified comparisons between its generic drug and the innovator drug for the purpose of satisfactorily meeting the conditions set out in Division 8 of Part C of the *Food and Drug Regulations* in order to obtain a notice of compliance for the generic drug.

[6] The *NOC Regulations*, adopted pursuant to section 55.2 of the *Patent Act*, R.S.C. 1985, c. P-4, allow an innovator who files a new drug submission to also submit to the Minister of Health a patent list relating to the submission. A patent on this list may then be added to a register of patents maintained by that Minister.

[7] A generic drug manufacturer who seeks a notice of compliance in respect of a drug and which compares that drug with another drug marketed in Canada under a notice of compliance must, with respect to each patent listed on the register for that other drug, either accept that it will not obtain the Minister's approval until the patent expires, or allege (through what is known as a "Notice of Allegation") that the patent is not valid or would not be infringed, and include a detailed statement of the legal and factual basis for the allegation: section 5 of the *NOC Regulations*.

[8] An innovator that is served with such a Notice of Allegation may apply to the Federal Court for an order prohibiting the Minister of Health from issuing a notice of compliance to the generic manufacturer until after the expiration of its patent. The court must make such an order if it finds

that the allegations relating to that patent and contained in the Notice of Allegation are not justified: section 6 of the *NOC Regulations*.

[9] The Supreme Court of Canada and our Court have determined that such an application is a highly fact specific summary proceeding, the sole object of which is to prohibit the issuance of a notice of compliance under the *Food and Drug Regulations*. Consequently, issues of patent infringement or validity cannot be finally determined in such a proceeding: *Eli Lilly & Co. v. Novopharm Ltd.*, [1998] 2 S.C.R. 129 at paras. 95-96; *Merck Frost Canada Inc. v. Canada (Minister of Health and Welfare)* (1994), 55 C.P.R. (3d) 302 (F.C.A.) at pp. 319-20; *David Bull Laboratories (Canada) Inc. v. Pharmacia Inc.*, [1995] 1 F.C. 588 (C.A.) at p. 600.

[10] If the innovator is successful in the proceeding, the Minister of Health is prohibited from issuing to the generic a notice of compliance for its generic drug until the relevant patent has expired. If the generic is successful, the Minister may issue a notice of compliance for its generic version of the drug. Whatever the outcome of the proceeding under the *NOC Regulations*, patent validity and patent infringement proceedings under the *Patent Act* may be initiated or continued by the parties before any competent court.

[11] In this case, Aricept has been approved by the Minister of Health, and notices of compliance have been issued for its oral administration in 5 and 10 mg doses for the symptomatic treatment of patients with mild, moderate and severe dementia of the Alzheimer's type. At Pfizer's request, the

‘808 Patent is listed in respect of Aricept on the register of patents maintained by the Minister of Health under the *NOC Regulations*.

[12] In 2009, Mylan (then doing business as Genpharm ULC) filed with the Minister of Health an abbreviated new drug submission for a notice of compliance in respect of a generic version of Aricept for oral administration in 5 and 10 mg doses. Mylan also served a Notice of Allegation challenging the validity of the ‘808 Patent on various grounds.

[13] Pfizer and Eisai responded by filing an application before the Federal Court seeking an order under section 6 of the *NOC Regulations* prohibiting the Minister from issuing a notice of compliance to Mylan.

The judgment of the Federal Court

[14] The issues before the Federal Court were reduced to the following question phrased as follows by the application judge at paragraph 35 of his Reasons: “*Is the ‘808 Patent, and in particular, claim 6 and claim 18, invalid because it is based upon an unsound prediction of the promised utility?*”

[15] Claims 6 and 18 of the ‘808 Patent read as follows, with the simplified version of those claims (as determined by the application judge) reproduced in brackets:

> 6. The compound 1-benzyl-4-[(5,6-dimethoxy-1-indanon)-2-yl] methylpiperidine or a pharmaceutically acceptable acid addition salt thereof.
>
> [6. The compound donepezil or donepezil hydrochloride.]

> 18. A therapeutical composition for treating senile dementia, which comprises an acetylchlolinesterase inhibitory effective amount of the compound or salt defined in any one of the claims 1 through 17 and a pharmaceutically acceptable carrier.
>
> [18. A therapeutical composition for treating senile dementia, which comprises donepezil or donepezil hydrochloride and a pharmaceutically acceptable carrier.]

[16] The application judge found that in the mid 1980's, it was hypothesized that if acetylcholinesterase ("AChE") inhibitors could be introduced into the appropriate area of the brain by crossing what is designated the Blood Brain Barrier, the symptoms of Alzheimer's disease may be alleviated. The application judge also found that, by June 1988 (the month during which the application for the '808 Patent was filed), two particular compounds were known and studied for this purpose: physostigmine and tacrine. However, though both these compounds appeared to work as AChE inhibitors, they had drawbacks: physostigmine had a short duration of action and certain undesirable side effects, while tacrine exhibited liver toxicity at higher doses.

[17] The application judge further found that work began at Eisai in the 1980's for the development of a drug for the treatment of senile dementia such as Alzheimer's disease, and that many compounds were tested for this purpose. Within this research effort, donepezil was developed at Eisai as a new compound, and it was found through tests on animals to act as an effective AChE inhibitor. This compound and its predicted use as a treatment for senile dementia were consequently patented by Eisai.

[18] The application judge concluded "that the 'promise' or stated utility of the '808 Patent" was "that a new class of compounds has been discovered (donepezil being one) which, having regard to the cholinergic function theory of AChE inhibition, is effective for the treatment of Alzheimer's": Reasons at para. 232. He came to that conclusion after reviewing the specification of the '808 Patent (at paras. 20 to 34 of the Reasons), considering how a person skilled in the art or science to which the invention pertains would read and understand the patent at the relevant time (paras. 189, 215 to 217 of the Reasons), extensively canvassing the concepts of "utility", "promise of the patent" and "sound prediction" (at paras. 199 to 231 of the Reasons), and taking all of the expert evidence into consideration.

[19] The application judge further found that even though donepezil's utility had not been demonstrated through testing on humans, its promised utility could be soundly predicted as of the filing date of the '808 Patent (June 21, 1988). Applying the test set out in *Apotex Inc. v. Wellcome Foundation Ltd.*, 2002 SCC 77, [2002] 4 S.C.R. 153 ("*Wellcome*") - that for there to be a "sound prediction", there must be a factual basis for the prediction, an articulable and sound line of reasoning from which the desired result can be inferred from the factual basis, and proper disclosure - the application judge found that a factual basis existed in that "donepezil was made and was tested in various ways in both mice and rats" (Reasons at para. 241); he was also satisfied that there was an articulable and sound line of reasoning that, as of June 1988, would have been considered to be *prima facie* reasonable in predicting the utility of donepezil as an AChE inhibitor and thus, in accordance with a reasonable scientific theory of the time (the cholinergic function theory of AChE inhibition) useful in treating senile dementia such as Alzheimer's: Reasons at paras. 242 to 244.

[20] As for the third requirement for sound prediction – proper disclosure – the application judge found that the factual basis and the articulable and sound line of reasoning had been properly disclosed in the patent (Reasons at paras. 241 and 244). He specifically found that the evidence of the experts, taken reasonably, showed that the disclosure made in the specification of the ‘808 Patent was sufficient to support the conclusion that donepezil is a good AChE inhibitor: Reasons at para. 245.

[21] He refused to consider Mylan’s submission that the disclosure was not sufficient because some of the data disclosed was allegedly wrong or misleading. He came to that conclusion on the ground that this issue had not been raised in Mylan’s Notice of Allegation and could not therefore be considered: Reasons at paras. 194 to 198 and 245. He further discarded Mylan’s allegation that the disclosure as to the toxicity of donepezil was inadequate, finding that lack of toxicity was not part of the promise of the patent and was not a necessary requirement in order to demonstrate utility: Reasons at paras. 246 and 247.

The issues on appeal

[22] Though Mylan is raising four issues in this appeal, these can be subsumed into two issues restated as follows:

a. Did the application judge err in finding that he could not consider Mylan’s assertion that wrong or misleading data were included in the ‘808 Patent, and, in the

affirmative, is Mylan's allegation of the patent's invalidity justified for lack of disclosure of the factual basis for its predicted utility?

b. Did the application judge err in failing to find that the '808 Patent promised that donepezil would have acceptable toxicity and be safer and longer acting than prior art compounds, and in the affirmative, is Mylan's allegation of the patent's invalidity justified for failure to disclose a factual basis sufficient to soundly predict such a promise?

First issue: Did the application judge err in finding that he could not consider Mylan's assertion that wrong or misleading data were included in the '808 Patent, and, in the affirmative, is Mylan's allegation of the patent's invalidity justified for lack of disclosure of the factual basis for its predicted utility?

[23] A number of arguments are advanced in relation to this issue. First, Mylan argues that there was a breach of procedural fairness when, at the hearing, the application judge raised, of his own initiative, the issue of the scope of the Notice of Allegation, and did not, allegedly, provide Mylan with an opportunity to properly respond. Second, Mylan argues that, fairly read, its Notice of Allegation does include the allegation that wrong or misleading data were included in the '808 Patent. Finally, Mylan argues that since wrong or misleading data were included in the '808 Patent, the disclosure in that patent could not disclose a factual basis sufficient to soundly predict its promised utility.

Procedural fairness

[24] Procedural fairness is a question of law reviewable on appeal on a standard of correctness: *G.D. Searle & Co. v. Novopharm Limited*, 2007 FCA 173, [2008] 1 F.C.R. 529, 58 C.P.R. (4th) 1 at para. 34; *Housen v. Nikolaisen*, 2002 SCC 33, [2002] 2 S.C.R. 235 at paras. 8-9.

[25] Mylan acknowledges that the application judge raised the issue of the scope or sufficiency of its Notice of Allegation and put the parties on notice of this issue at the outset of the hearing. Mylan did respond by arguing to the application judge the reasons why, in its view, its Notice of Allegation included the allegation that wrong or misleading data were reported in the '808 Patent. Mylan does not allege that it should have been allowed to submit additional evidence on the issue. It rather submits that the application judge should have invited written submissions (Mylan's Memorandum at para. 41). However, Mylan does not allege that it made a request to the application judge to provide additional written representations on the issue.

[26] Mylan is thus left with its submission that by "independently raising and then deciding the issue of sufficiency, Justice Hughes breached the requirements of procedural fairness" (Mylan's Memorandum at para. 42).

[27] A judge must decide a case according to the facts and the law as he finds them to be. Accordingly, there is no procedural unfairness where a judge, on his own initiative, raises and decides an issue in a proceeding, as long as, of course, that he has informed the parties of that issue and has given them a fair opportunity to respond: *Murphy v. Wyatt*, [2011] EWCA Civ 408, [2011]

1 WLR 2129 at paras. 13 to 19; *R. v. Keough*, 2012 ABCA 14 at para. 20; *R v. Fraillon* (1990), 62 C.C.C. (3d) 474 (Q.C.A.) at para. 7.

[28] It is not disputed that the application judge in this case informed the parties of the issue and gave them an opportunity to respond at the hearing, and that Mylan availed itself of this opportunity. In these circumstances, I cannot find that the application judge breached the rules of procedural fairness by deciding the matter as he did.

The allegations included in the Notice of Allegation

[29] It is well established that a Notice of Allegation frames the proceeding under the *NOC Regulations*, and that any allegation which is not included in that notice cannot be addressed in the proceeding: see subparagraph 5(3)(*b*)(ii) of the *NOC Regulations*, which requires that the Notice of Allegation include "a detailed statement of the legal and factual basis for the allegation"; see also *Mayne Pharma (Canada) Inc. v. Aventis Pharma Inc.*, 2005 FCA 50, 38 C.P.R. (4th) 1 at para. 21; *AB Hassle v. Canada (Minister of National Health and Welfare)* (2000), 7 C.P.R. (4th) 272 (F.C.A.) at paras. 16 to 23; *AB Hassle v. Apotex Inc.*, 2006 FCA 51, [2006] 4 F.C.R. 513, 47 C.P.R. (4th) 329 at para. 4; *Ratiopharm Inc. v. Canada (Health)*, 2007 FCA 83, *sub nom. Abbott Laboratories v. Canada (Minister of Health)*, 58 C.P.R. (4th) 97 at paras. 23-24. The special proceedings under the *NOC Regulations* are meant to be summary. There is no discovery phase, and the proceedings are thus necessarily limited to the legal grounds and specific factual allegations set out in a Notice of Allegation, which cannot be subsequently amended. This is a well understood feature of a proceeding under the *NOC Regulations*.

[30] It is also well settled that the sufficiency of a Notice of Allegation is a question of mixed fact and law, and that no determination of this issue is to be disturbed on appeal unless a palpable and overriding error can be found, except to the extent that a question of law can be extricated from the determination, in which case that question is reviewable on a correctness standard: *Pfizer Canada Inc. v. Apotex Inc.*, 2004 FCA 398, 38 C.P.R. (4th) 400 at para. 25; *AstraZeneca AB v. Apotex Inc.*, 2005 FCA 183, 39 C.P.R. (4th) 289 at para. 9; *Novopharm v. Pfizer Canada Inc.*, 2005 FCA 270, 42 C.P.R. (4th) 97 at para. 11; *AB Hassle v. Apotex Inc.*, above at para. 17; *Pharmascience Inc. v. Sanofi-Aventis Canada Inc.*, 2006 FCA 229, [2007] 2 F.C.R. 103, 53 C.P.R. (4th) 357 at para. 15. Though the parties disagree on many issues in this appeal, they nevertheless agree that the standard of review applicable to a determination of the scope of a Notice of Allegation is the one described above.

[31] The scope of the allegations which are included in a Notice of Allegation must be determined in each case in view of the language of the Notice of Allegation at issue as well as the evidence submitted. Each case is different and highly fact-specific.

[32] In this case, the application judge found that the issue of whether the data disclosed in the patent accurately reflected the work carried out by Eisai had not been raised by Mylan in its Notice of Allegation. Before reaching this conclusion, he clearly appreciated that Mylan could not have been aware of the facts underlying such an allegation until it had access to Eisai's testing results. These results were only provided to Mylan after its Notice of Allegation had been served. Mylan

could thus not have included in its Notice of Allegation an allegation that the data disclosed in the patent did not reflect the work carried out at Eisai since "without actual knowledge as to what went on at Eisai at the time, Mylan would have no basis for making such allegations" (Reasons at para. 196). The application judge thus correctly found that this allegation was only raised by Mylan after its Notice of Allegation had been served, and only after Pfizer had disclosed various testing data in response to that notice.

[33] Mylan however also contends that the application judge should have given a broad interpretation to its Notice of Allegation in view of the fact both Eisai and Pfizer had an opportunity to file evidence from their own experts to support their contention that the errors or discrepancies in the data were minor and irrelevant. Consequently, Mylan submits that Eisai and Pfizer were not prejudiced by Mylan's allegation relating to the accuracy of the patent data. Mylan cites two decisions of the Federal Court in support of this submission: *Pfizer Canada Inc. v. Canada (Health)*, 2008 FC 13, 64 C.P.R. (4th) 1 at paras. 45 to 49, and *AstraZeneca Canada Inc. v. Mylan Pharmaceuticals ULC*, 2011 FC 1023, 96 C.P.R. (4th) 159 at paras. 70 to 79. However, Eisai and Pfizer point to other Federal Court decisions which do not support Mylan's submission on this point: *Pfizer Canada Inc. v. Canada (Minister of Health)*, 2006 FC 1471, 54 C.P.R. (4th) 279 at paras. 66 to 72; *Merck Frost Canada Inc. v. Canada (Minister of Health)* (2000), 8 C.P.R. (4th) 87, [2000] F.C.J. No. 785 (QL) at para. 12, aff'd 2001 FCA 192, 12 C.P.R. (4th) 447. Since the scope of a Notice of Allegation is largely dependent on its wording and on the particular facts of each case, the discordance in the Federal Court jurisprudence is more apparent than real, since each case turns on its own particular circumstances.

[34] In this case, the application judge found that Mylan's Notice of Allegation did not contain an allegation as to whether the '808 Patent fully and accurately set out the work done by Eisai: Reasons at paras. 196 and 197. The pertinent extracts of Mylan's Notice of Allegation are set out in an annex to the Reasons. Upon a fair reading of that document, the application judge concluded that Mylan did not allege that the work done at Eisai was not fully and accurately set out in the patent. That finding was not based on a palpable and overriding error. Consequently, it should not be disturbed on appeal.

[35] In any event, and as further discussed below, even if the application judge had considered Mylan's submissions on the issue of the data discrepancies, this would not have resulted in the outcome sought by Mylan.

The alleged data discrepancies

[36] In the light of the record as constituted in these proceedings, the alleged data discrepancies are not material to the '808 Patent when considered in the overall context of the invention and what is disclosed by the patent. It is noteworthy that the application judge largely discarded the evidence of Mylan's sole expert on the issue, Dr. Becker, on the basis that his evidence was seriously flawed. In particular, it was found that Dr. Becker had "been urged by Mylan's former Counsel into acting as an advocate": Reasons at para. 243.

[37] The ‘808 Patent discloses that donepezil was tested *in vitro* in a mouse brain homogenate and *ex vivo* in rats, and these tests show that it is a strong and potent AChE inhibitor. However, while some of the compounds studied through the *in vitro* testing were tested using mouse brain homogenate, the *in vitro* testing for donepezil reported in the patent was carried out using rat brain homogenate. This is one of the alleged data discrepancies raised by Mylan.

[38] However, the evidence in the record of the proceeding is abundantly clear: for a person skilled in the art or science to which the invention pertains, *i.e.*, “someone with an advanced degree in medical chemistry, biology or pharmacology, or a clinician working in the area of dementia” (Reasons at para. 189), this error is not material and does not affect the conclusions reached in the patent. The application judge accepted Dr. Bartus’ expert evidence and his conclusion (at para. 122 of his affidavit) that the testing reporting error (mouse brain homogenate vs. rat brain homogenate) did not change the conclusion that donepezil exhibits potent AChE inhibitory activity: Reasons at paras. 57, 242 and 243. Dr. Bartus is the Executive Vice President and Chief Scientific Officer of a biotechnology company, an adjunct professor in the department of pharmacology at Tufts University Medical Center in Boston, as well as an adjunct professor in the department of psychiatry at the New York University Medical Center. Dr. Bartus stated the following at paragraph 122 of his affidavit:

> …The *in vitro* AChE inhibitory activity data on the rat and mouse brain homogenate establish that it really does not matter whether rat or mouse brain homogenates were used; the outcomes are essentially the same (*i.e.*, equivalent) and the underlying conclusions/interpretations are the same (*i.e.*, that donepezil is a potent compound). [Affidavit of Dr. Bartus, para, 122, reproduced at p. 2984 of the Appeal Book]

[39] A second data reporting error raised by Mylan concerns the testing on rats that Eisai conducted in order to assess the action of donepezil on passive avoidance learning impairment induced by scopolamine and reported in table 3 of the '808 Patent. The patent states that the test compounds were administered one hour before the training trial and that the rats had been previously treated with a 0.5 mg/kg dose of scopolamine, while the results shown are actually for testing of compounds which were administered two hours before the training trial with the rats being previously treated with a 1.0 mg/kg dose of scopolamine. Again, this reporting error has little significance, being qualified as "a trivial point" by Dr. Bartus in his cross-examination: transcript of answer to question 1001, Appeal Book at pp. 3746-3747.

[40] The application judge accepted Dr. Bartus' expert evidence that these testing result reporting errors were not material [para. 60 of the Reasons]:

> [60] Dr. Bartus acknowledged that the description of Example 3 of the '808 Patent (page 50 of the patent) contained an error – i.e. the test was conducted at a doses (*sic*) of 1.0 mg/kg of scopolamine and donepezil had been administered two hours before training; not 0.5 mg/kg, one hour before training. Dr. Bartus did not consider the error material:
>
> > *Having seen the data where donepezil had been administered one hour before training in the Ogura Affidavit (i.e., 16% at 0.25 mg/kg and 51% at 0.5 mg/kg) the conclusion that donepezil is able to reverse scopolamine-induced cholinergic deficit both at one hour and two hours supports the conclusion that donepezil is a compound that is capable of reversing the cholinergic deficit caused by scopolamine.* [Affidavit of Dr. Bartus, para. 149, reproduced at p. 2993 of the Appeal Book]
>
> [Emphasis added]

[41] The application judge also accepted the expert evidence of Dr. Rockwood, a professor of Geriatric Medicine & Neurology at Dalhousie University, who holds the title of Kathryn Allen

Weldon Professor of Alzheimer Disease Research. Dr. Rockwood specifically stated in his affidavit that these discrepancies were not material to the conclusion that any skilled person would draw [paragraph 94 of the Reasons]:

> [94] Dr. Rockwood stated the data in the '808 Patent sufficiently discloses the factual basis in order to make a sound prediction. He highlights the following disclosure:
>
> …
>
> Table 3 of the '808 Patent (page 52) and the results of compound 4 (i.e. donepezil) – which teaches donepezil is able to reverse the cholinergic deficit, regardless of the error in data (i.e. the compound was tested after two hours at a 1.0 mg/kg dose, not after one hour at a 0.5 mg/kg dose).
>
> [Affidavit of Dr. Rockwood, para. 58, reproduced at pp. 3929-3930 of the Appeal Book]
>
> [Emphasis added]

[42] Dr. Rockwood expressed himself as follows at subparagraph 58(c) of his affidavit referenced approvingly by the application judge at paragraph 94 of his Reasons reproduced above:

> …My conclusion that donepezil reverses the cholinergic deficit induced by scopolamine would not change even if the inventors had used a dose of 1.0 mg/kg of scopolamine (instead of the 0.5 mg/kg dose described in the 808 Patent) or if donepezil had been administered two hours before training (instead of the one hour described in the 808 Patent). These differences described are not material to the conclusion any skilled person would draw. [Affidavit of Dr. Rockwood, subparagraph 58(c), reproduced at p. 3930 of the Appeal Book]
>
> [Emphasis added]

[43] The third error raised by Mylan concerns the toxicity data. The ‘808 Patent indicates that representative compounds of donepezil were applied to toxicity tests on rats, and “[a]s a result, all compounds exhibited a toxicity of 100 mg/kg or more, i.e., exhibited no serious toxicity”: page 54 of ‘808 Patent reproduced at page 230 of the Appeal Book. However, rats were not tested by Eisai

at a dose of 100mg/kg, but rather at doses of 3mg/kg, 10mg/kg and 30 mg/kg. Suji Sumigama, who was involved at Eisai with the toxicity testing of donepezil, noted in his affidavit that "there was no irreversible toxic effects at these dose amounts"; but that "[t]he degree of peripheral symptoms, including fasciculation, increased at 30 mg/kg, which suggested to me that donepezil would be lethal in rats at the next dosage increment (*i.e.*, 100 mg/kg)": Affidavit of Suji Sumigama at para. 18, reproduced at p. 2221 of the Appeal Book.

[44] Dr. McKenna holds a PhD in toxicology and has over 35 years of experience in toxicology and pharmaceutical drug development, including overseeing the development of tacrine, another AChE inhibitor. Dr. McKenna found no disagreement between the Sumigama affidavit and the statement in the '808 Patent with respect to serious toxicity: Affidavit of Dr. McKenna, para. 67, reproduced at pp. 4893-4894 of the Appeal Book.

[45] The application judge accepted the expert testimony of Dr. McKenna confirming that this was a reasonable conclusion to make, and that it was consistent with, and supportive of, the statement made in the patent that donepezil "exhibited toxicity of 100 mg/kg or more, *i.e.*, exhibited no serious toxicity." [at para. 121 of the Reasons]:

> [121] Dr. McKenna reviewed the Chosa Hokoku Report which included the results of a one and four week test in rats and dogs as described by Dr. Sumigama. To Dr. McKenna it was reasonable for Dr. Sumigama to conclude that 100 mg/kg would have caused serious toxicity, regardless if it is not demonstrated in the report or '808 Patent:
>
> > *[54] With reference to the '808 Patent it is my opinion that it was reasonable for Mr. Sumigama to conclude, based on his observation at 30 mg/kg in rats (at which point no "serious" toxicity had been observed), that serious (i.e., irreversible) toxicity would be observed at 100 mg/kg, which was the next incremental dose that would have been tested. This conclusion*

> *is consistent with and supports the statement in the patent that donepezil "exhibited toxicity of 100 mg/kg or more, i.e., exhibited no serious toxicity." This statement means that there are no serious toxicity concerns at doses of less than 100 mg/kg, but at doses of 100 mg/kg or more, donepezil exhibits serious toxicity. This was the conclusion reached by Mr. Sumigama and it was an entirely reasonable conclusion to make.* [Affidavit of Dr. McKenna, para. 54, reproduced at pp. 4889-4890 of the Appeal Book]

[46] Therefore, the three data discrepancies that Mylan invokes are not material. The expert evidence in the record is overwhelming in this regard. The minor *bona fide* data reporting errors do not materially change the results reported in the patent, nor do they affect the inference which a person skilled in the art or science to which the invention pertains would reasonably draw from these reported results. The data in the '808 Patent informs the skilled person that donepezil is a compound that inhibits AChE and can be soundly predicted to treat Alzheimer's disease.

[47] In conclusion, I find no merit to any of Mylan's contentions on the first issue raised in this appeal.

Second Issue: Did the application judge err in failing to find that the '808 Patent promised that donepezil would have acceptable toxicity and be safer and longer acting than prior art compounds, and, in the affirmative, is Mylan's allegation of the patent's invalidity justified for failure to disclose a factual basis sufficient to soundly predict such a promise?

[48] The promise of a patent is a question of law reviewable on appeal on a standard of correctness, though generally, the construction of the promise is an exercise that requires the assistance of expert evidence, as the promise should be properly defined, within the context of the patent as a whole, through the eyes of a person skilled in the art or science to which the invention

pertains: *Eli Lilly Canada Inc. v. Novopharm Limited*, 2010 FCA 197, 85 C.P.R. (4th) 413 at para. 80.

[49] Mylan submits that the application judge erred in finding that, though the patent promises an effective treatment for Alzheimer's disease, such a promise did not require that donepezil have an acceptable toxicity in humans at effective doses. Mylan adds that the application judge also erred in not finding that the promise of the invention was that donepezil would have better toxicity and duration of action than prior art compounds such as physostigmine and tacrine. These alleged errors are interrelated, since Mylan is essentially arguing that both the toxicity and efficacy of donepezil were part of the promise of the '808 Patent.

[50] Mylan further submits that the data presented in the '808 Patent (a) are insufficient for a sound prediction of a level of safety in humans that would allow for the therapeutic utility of donepezil; and (b) do not disclose a factual basis that can support a sound prediction of better toxicity and duration for donepezil as compared to prior art compounds.

[51] Mylan's submission concerning the insufficiency of the data presented in the patent depends on the construction of the promise of the patent. In other words, I must first accept Mylan's submission that the application judge erred in construing the promise as he did before addressing Mylan's insufficiency of data submission.

[52] As noted above, the application judge held that the promised utility of the ‘808 Patent was “that a new class of compounds has been discovered (donepezil is one) which, having regard to the cholinergic function theory of AChE inhibition, is effective in the treatment of Alzheimer’s”: Reasons at para. 232. As mentioned earlier, the application judge reached this conclusion by applying the correct test: Reasons at paras. 212 to 218.

[53] The application judge, following the decision of the Supreme Court of Canada in *Wellcome*, further concluded that “proof of lack of toxicity at this stage is not a necessary requirement in order to demonstrate utility”: Reasons at para. 247. In *Wellcome*, the patent in issue pertained to the use of AZT for the treatment and prophylaxis of HIV/AIDS. The appellants in that case argued that “[b]efore it could be known whether AZT could be used as a treatment for HIV in humans, …Glaxo/Wellcome needed to know if AZT would be absorbed into the human blood stream, make its way to the T-cells infected with HIV, enter the T-cells and inhibit the reproduction of the HIV infection without proving toxic to other cells, and demonstrate clinical improvement in the patient”: *Wellcome* at para. 20. This argument was rejected by the Supreme Court of Canada. Binnie J., writing for the Court, observed at paragraph 3 of *Wellcome*:

> …It was sufficient that at that time the Glaxo/Wellcome scientists disclosed in the patent a rational basis for making a sound prediction that AZT would prove useful in the treatment and prophylaxis of AIDS, which it did. For the Commissioner of Patents to have allowed Glaxo/Wellcome a patent based on speculation would have been unfair to the public. For him to have required Glaxo/Wellcome to demonstrate AZT’s efficacy through the clinical tests required by the Minister of Health for approval of a new drug for medical prescription would have been unfair to Glaxo/Wellcome. …

[54] Binnie J. specifically rejected the argument that utility must be demonstrated by prior human trials establishing toxicity and other factors, concluding instead that "[t]he prerequisites of proof for a manufacturer who wishes to market a new drug are directed to a different purpose than patent law. The former deals with safety and effectiveness. The latter looks at utility, but in the context of inventiveness. The doctrine of sound prediction, in its nature, presupposes that further work remains to be done": *Wellcome* at para. 77.

[55] Mylan does not dispute that acceptable toxicity is not a requirement for patentability: Mylan's Memorandum at para. 75. Rather, Mylan argues that where a patentee promises that a compound will be free from negative side effects or has better toxicity and duration than prior art compounds, the patentee will be held to that promise. It cites *Apotex Inc. v. Pfizer Canada Inc.*, 2011 FCA 236, 95 C.P.R. (4th) 193 ("*Latanoprost*") in support of this last proposition. The difficulty with Mylan's argument is that the patent in this case bears no similarity to the one considered in *Latanoprost*.

[56] The patent in *Latanoprost* claimed a "therapeutic composition for topical treatment of glaucoma or ocular hypertension, containing a prostaglandin…in an amount sufficient to reduce intraocular pressure without causing substantial ocular irritation…": *Latanoprost* at para. 8 [emphasis added]. In this unique circumstance, where the patent appeared to be premised on avoiding the disadvantage associated with side effects, this Court construed the patent considered in *Latanoprost* as promising the avoidance of side effects. In contrast, claim 18 of the '808 Patent simply refers to a " therapeutical composition for treating senile dementia…" without any further

promise relating to side effects or toxicity. There is no relation between the ‘808 Patent and the patent reviewed in *Latanoprost*. The ‘808 Patent is rather akin to the patent reviewed by the Supreme Court of Canada in *Wellcome.*

[57] Though some references are made in the ‘808 Patent to potential toxicity and efficacy benefits of donepezil, and to its potential advantages over prior art compounds, the application judge, on the basis of the expert evidence before him, rightly concluded that these references are not to be construed as promises. He noted that the use of the specification of a patent in order to construe its promise “is not to serve as an invitation to a zealous lawyer to read a patent specification in such a way as to persuade a Court, one way or the other, as to what the promise is”: Reasons at para. 213. As recently aptly noted by Zinn J. of the Federal Court, “the jurisprudence does not permit an unescorted and unchaperoned romp through the disclosure”: *Janssen-Ortho Inc. v. Canada (Health)*, 2010 FC 42, 82 C.P.R. (4th) 336 at paras. 119-120. The disclosure in the specification is to be understood from the viewpoint of a skilled person in the art or science to which the invention pertains, without resort to technicalities but rather for the purpose of seeking a construction of the claims which is reasonable and fair for both the patentee and the public: *Consolboard Inc. v. MacMillan Bloedel (Sask.) Ltd.*, [1981] 1 S.C.R. 504 at pp. 520-21.

[58] In this case, the expert evidence as to what a person skilled in the art or science pertaining to the invention would have understood as the promise of the ‘808 Patent overwhelmingly confirms the application judge’s construction of that promise.

[59] As noted by the application judge at paragraph 53 of his Reasons, Dr. Bartus rejected Mylan's list of promises set out in its Notice of Allegation, and was of the view that a skilled person would understand these as potential advantages of donepezil, not as patent promises. Though Dr. Bartus' comments focus on the disputed claims 6 and 18 of the '808 Patent, the application judge rightly understood these comment as pertaining to the patent as a whole:

> [53] Dr. Bartus rejected Genpharm's (Mylan's) list of promises as set out in the Notice of Allegation and characterized any such promise as potential advantages of the '808 Patent:
>
> > *I do not think that a skilled person would fairly read this Patent in that way. Rather, a skilled person would understand that what the inventors are saying about claim 6 is that it is an AChE inhibitor that can cross the BBB* [Blood Brain Barrier]. *The other statements in the Patent are either statements of potential advantages (such as low toxicity, bioavailability, good physical properties) which a skilled person would see as a helpful description but not a promise, or indicators of what one might do with an AChE inhibitor. These latter statements include a predicted use for treating senile dementia, which is the promise of claim 18.* [Affidavit of Dr. Bartus, para. 101, reproduced at pp. 2976-2977 of the Appeal Book]

[60] At paragraph 54 of his Reasons, the application judge also accepted Dr. Bartus' expert evidence, stated at paragraphs 102 and 104 of his affidavit, that a skilled person would understand the promise of the '808 Patent as a promise for treatment of senile dementia in humans. However, as Dr. Bartus noted in his affidavit, such a promise does not extend to toxicity and efficacy. The relevant parts of his affidavit read as follows:

> 102. … the therapeutic use which the Patent promises is a predicted use, in the sense that the compound (at least based on the data in the Patent) had not yet been tested in humans. The skilled person would not expect that this compound would yet have been tested in humans. In fact, there are usually many years between patent filing and final regulatory approval, during which time a whole battery of other tests involving biologists, pharmacologists, pharmacokineticists, pharmaceutical scientists and toxicologists, as well as all the clinical trials required to demonstrate safety and efficacy in humans would have been conducted.

> …
>
> 104. … Some degree of toxicity is inevitable with any drug, but whether the toxicity is acceptable or unacceptable will ultimately be a question answered only after clinical trials. Similarly, formulation, pharmacokinetics and other issues will need to be worked out over time, and a skilled person would not read any of these attributes into the 808 Patent.
>
> [Affidavit of Dr. Bartus, paras. 102 and 104, reproduced at pages 2977-2978 of the Appeal Book]

[61] The other expert opinions accepted by the application judge were to the same effect. Dr. Rockwood reviewed the data in the ‘808 Patent and concluded that a skilled person would not understand as a promise donepezil’s noted advantages of duration and safety with respect to prior art compounds: Reasons at para. 93. Likewise, Dr. McKenna characterized the patent references to toxicity and safety as only instructive, and these references would not amount, for a skilled person, to a promise of the patent: Reasons at paras. 117 to 120 and 246.

[62] The application judge acted cautiously in assessing this expert evidence and came to his own sound conclusion as to the promise of the patent: Reasons at paras. 41, 218 and 232. Having considered the ‘808 Patent, and on the basis of the record before me, I am unable to find any error in his conclusion.

[63] Having concluded that the application judge committed no error in construing as he did the promise of the ‘808 Patent, I need not consider Mylan’s submission that the data presented in the ‘808 Patent are insufficient to allow for a sound prediction of a level of toxicity in humans and of better toxicity and duration than prior art compounds. Furthermore, in the light of this conclusion, I need not consider Pfizer’s and Eisai’s alternative submissions that claim 6 can be construed

separately from claim 18, and that claim 6 simply concerns a compound which exhibits AChE inhibition properties.

[64] I note in closing that the determination of the soundness of the prediction is a question of fact, reviewable on appeal on a standard of overriding and palpable error: *Wellcome* at para. 71. In this case, the application judge found that the prediction made in the '808 Patent as he construed it – that donepezil is effective for the treatment of Alzheimer's – was sound having regard to the cholinergic function theory of AChE inhibition. The application judge's conclusion is amply supported by the abundant evidence which was before him: Reasons at paras. 65 to 69, 72, 88 to 90 and 94-95.

Conclusions

[65] For the reasons set out above, I would dismiss this appeal. I would also award costs in this appeal to Pfizer and Eisai.

"Robert M. Mainville"
J.A.

"I agree.
K. Sharlow J.A."

"I agree.
Johanne Gauthier J.A."

FEDERAL COURT OF APPEAL

NAMES OF COUNSEL AND SOLICITORS OF RECORD

DOCKET:	A-226-11
APPEAL FROM AN ORDER OF MR. JUSTICE HUGHES OF THE FEDERAL COURT DATED MAY 12, 2011.	
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PLACE OF HEARING:	Ottawa, Ontario
DATE OF HEARING:	February 22, 2012
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CONCURRED IN BY:	SHARLOW J.A. GAUTHIER J.A.
DATED:	March 29, 2012

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