Federal Court  Cour fédérale

Date: 20110713

Docket: T-1165-09

Citation: 2011 FC 875

Vancouver, British Columbia, July 13, 2011

PRESENT: The Honourable Mr. Justice O'Reilly

BETWEEN:

HOFFMANN-LA ROCHE LIMITED

Applicant

and

APOTEX INC. AND THE MINISTER OF HEALTH

Respondents

and

ROCHE PALO ALTO LLC

Respondent / Patentee

REASONS FOR JUDGMENT AND JUDGMENT

I. Overview

[1] Hoffman-La Roche Ltd. [Roche] asks me to order the Minister of Health not to issue a Notice of Compliance [NOC] to Apotex Inc. The NOC would permit Apotex to market a generic

version of a drug, mycophenolate mofetil [MMF], for which Roche has a patent [Canadian Patent 1,333, 285 – the ‘285 patent]. Roche markets MMF under the brand name CellCept. MMF is an immunosuppressive drug used primarily in organ transplants.

[2] Roche maintains that the Minister should not issue an NOC to Apotex until the expiry of the ‘285 patent, relying on the *Patented Medicines (Notice of Compliance) Regulations*, SOR/93-133, s 6 (enactments cited are set out in Annex A). Apotex alleges that the ‘285 patent is invalid, essentially because its subject matter does not constitute an invention. It submits, therefore, that it is entitled to an NOC and that Roche’s application should be dismissed.

[3] Because Apotex has presented probative evidence supporting its allegations, the burden falls on Roche to prove that Apotex’s allegations are unjustified.

[4] I am satisfied that Roche has met its burden. While Apotex asserts that MMF’s utility was neither demonstrated nor soundly predicted when Roche applied for its patent, and that MMF was an obvious variant on the prior art, I am satisfied that the preponderance of the evidence is to the contrary. I must, therefore, allow Roche’s application.

[5] There are two issues:

1. Was MMF’s utility demonstrated or soundly predicted?
2. Was MMF obvious?

II. Factual Background

[6] Immunosuppressive drugs inhibit the body's naturally antagonistic response to transplanted organs. These drugs operate by suppressing the cells, called T-cells and B-cells, that control the immune response. Mycophenolic acid [MPA] was a well-known compound that could be used as an immunosuppressive drug but, like many of these kinds of drugs, it had serious limitations, particularly, poor solubility and bioavailability.

[7] Because of these problems, scientists began, in the 1970s and 1980s, looking for ways to improve immunosuppressive drugs, including MPA. Various strategies were tried but the solution the inventors of the '285 Patent arrived at was to produce a prodrug of MPA. A prodrug is an inactive, closely-related compound to the parent drug that reverts to the active parent drug after ingestion. Roche created a prodrug of MPA by adding a morpholinoethyl (mofetil) ester group onto the MPA molecule. The resulting compound was mycophenolate mofetil – MMF - the subject of the '285 patent. In the body, MMF is absorbed, and then is metabolized to yield MPA, the active compound, by a process known as "ester hydrolysis".

III. The '285 Patent

[8] The application for the '285 Patent was filed December 15, 1987; the patent issued on November 29, 1994 and will expire November 29, 2011. It is entitled "Morpholinoethylester of

Mycophenolic Acid and Derivatives Thereof". While the patent includes fourteen claims, Roche is only asserting Claim 2 – a claim to the compound MMF.

[9] The patent states that the compounds of the invention are useful as "immunosuppressive and anti-inflammatory agents" and, based on "their effects on purine metabolism", they can be used to treat rheumatoid arthritis, and as "anti-tumor agents, anti-viral agents, and anti-psoriatic agents in mammals", and "preferably in humans". The patent goes on to declare that the compounds "have advantageous pharmacokinetic properties, for example, solubility in the delivery environment (*e.g.*, the stomach), peak plasma concentration, maximum plasma concentration, and improved activity, *e.g.*, anti-inflammatory activity as compared to mycophenolic acid."

[10] The patent contains a number of examples illustrating the properties of the invented compounds, some being *in vitro* studies, others being *in vivo*.

[11] Apotex sent Roche a Notice of Allegation [NOA] in May 2009, in which it alleged that the '285 patent was invalid mainly on grounds of obviousness and lack of utility.

IV. Construction of the '285 Patent

[12] To construe the patent, I must consider how it would be read by a person skilled in the relevant art. Here, the parties agree that the hypothetical skilled person would have a graduate degree in chemistry, be familiar with medicinal chemistry, drug discovery and formulation, particularly in respect of immunosuppressive agents, and have knowledge of research and

treatments relating to autoimmune disorders, psoriasis, inflammatory diseases, tumours and viral infections.

[13] The patent acknowledges that MPA was a known compound, and that esters of MPA were described in prior art as having anti-tumour, immunosuppressive, antiviral, anti-arthritic and anti-psoriatic properties. The patent also notes that ester derivatives of MPA could be prepared from commercially available MPA.

[14] As mentioned, the patent describes certain positive characteristics of MMF (and related compounds), namely, advantageous pharmacokinetic properties and improved activity as compared to MPA. “Advantageous pharmacokinetic properties” refers to characteristics such as solubility and maximum plasma concentration. These features are mentioned, presumably, to distinguish MMF from MPA, whose limited bioavailability reduced its value as an immunosuppressive drug. But it is also clear from the patent that the ultimate effect of MMF is the same as that of MPA, since MMF is metabolized into MPA after ingestion. The two compounds can be used for the same purposes and operate by the same method of action.

[15] Roche maintains, however, that the advantageous pharmacokinetic properties and the corresponding improved activity of MMF do not form part of the invention that is the subject matter of the ‘285 patent. Nor is there a specific promise of use in humans. Rather, the invention is MMF alone, and its utility is the same as MPA’s. The fact that MMF has advantages over MPA and other compounds, Roche says, is incidental to the invention.

[16] Roche contends that there is no requirement to state the advantages of an invention in a patent. An invention need only have a scintilla of utility to be patentable and, accordingly, a patent need only identify that utility. Inventors may go beyond their obligations and set out the advantages of an invention in a patent, but the Court should not penalize them for it by requiring them to prove that those advantages were demonstrated or soundly predicted when the patent was filed. Roche concedes that a higher utility requirement may arise in patents that promise a particular result, or in selection patents, where advantages over a previously patented class of compounds must be demonstrated or soundly predicted. However, for most patents, Roche argues, only a minimum level of utility is required.

[17] Apotex asserts that the patent should be construed as including a promise that MMF has those advantageous pharmacokinetic properties that make it superior to MPA alone and useful for the treatment of various conditions in mammals, particularly humans.

[18] I agree with much of Roche's submission. Usually, a patent holder need only show a scintilla of utility to satisfy the definition of an invention as a "new and useful" product (*Patent Act*, RSC 1985, c P-4, s 2). The exceptions relate to patents that promise a specific result, and selection patents, where advantages are required. However, I disagree with Roche to this extent – the task of construing a patent does not simply involve a search for that morsel of utility on which the patent holder hopes to rely. The Court must review the patent's specification with an eye to the essence of the invention, appreciating how a skilled person would interpret the words the inventor used to describe it.

[19] As Justice Roger Hughes put it, “in construing the specification of a patent, in particular the ‘promise’, the Court is to look at the specification through the eyes of a person skilled in the art, bearing in mind commercial realities, being neither benevolent nor harsh, in order to determine fairly the true intent” (*Pfizer v Mylan Pharmaceuticals*, 2011 FC 547, at para 217).

[20] Roche also asserted that a patent holder can rely on the advantages described in a patent to show that the invention was not obvious, even though those advantages are not relevant to utility. In my view, in construing a patent, the Court must identify the claimed invention – the purportedly new and useful thing. In analyzing the question whether the inventors have met the requirement of utility, the Court will consider whether the inventors have disclosed a “new article, a better article, a cheaper article, or affords the public a useful choice” (C*onsolboard Inc v MacMillan Bloedel (Sask) Ltd*, [1981] 1 SCR 504 at 521). In analyzing the question of whether the putative invention is, in fact, obvious, the Court must (among other things) consider whether the claimed invention consists of an inventive step over the common general knowledge in the field.

[21] I do not accept, as Roche urges on me, that these two inquiries are completely separate and unrelated. Both depend on a fair and neutral construction of the patent.

[22] In my view, construction of the patent is a preliminary step which precedes the analysis of the grounds of potential invalidity. It should be carried out without regard for the impact of the construction on utility or obviousness, or whatever other issues arise in the case (*Whirlpool Corp v Camco Inc*, 2000 SCC 67, at para 43). As Apotex argued, where advantages form part of the stated invention, it would be unfair to allow the patent holder to rely on those advantages to show that the

invention was unobvious and, at the same time, dismiss those advantages as being irrelevant to utility. A patent holder cannot read up the invention for obviousness and read it down for utility.

[23] With that approach in mind, as I read the patent, the inventors state that the compounds of the invention are useful as immunosuppressive and anti-inflammatory agents, and because of their anti-tumour, anti-viral, and anti-psoriatic effects. They go on (albeit a few pages later) to tout the compounds' advantages over MPA.

[24] I agree with Apotex's submission that the patent relates to compounds, particularly MMF, that not only possess the beneficial therapeutic properties of MPA but represent an improvement over MPA because of their pharmacokinetic advantages.

[25] This interpretation is supported by expert evidence on the point (Experts are identified in Annex B). For example, Dr. Johnson (an Apotex expert), stated that a skilled person "would understand from the '285 Patent as a whole that the compounds of Formula A [MMF] would show higher activity and advantageous pharmacokinetics in biological tests comparing them to mycophenolic acid" (para 60). Dr. Borch, another of Apotex's experts, agreed.

[26] While Roche's experts disagreed with this construction, they simply disputed that advantages could form part of an invention's stated utility. They agreed that the patent makes clear that MMF possesses advantageous pharmacokinetic properties (*e.g.*, Dr. Anderson, Dr. Sawchuk, and Dr. Cattral).

[27] Further, the co-inventors of the ‘285 Patent were clearly looking for a compound that would improve MPA’s bioavailability and felt they had found one in MMF, whose advantageous pharmacokinetic properties helped overcome MPA’s poor solubility (Dr. Lee and Dr. Allison). If MMF had not possessed those properties, it is unlikely the inventors would have believed they had invented anything.

[28] Therefore, reading the ‘285 patent as a whole, through the eyes of the skilled person, I find that the essence of the invention lies in the identification of a prodrug version of MPA. A prodrug is really a delivery system for a payload; here, MPA is the payload. The sole mission of MMF is to deliver MPA. MMF has no independent beneficial properties.

[29] Again, the reason why the inventors were looking for a prodrug for MPA was to try to improve MPA’s bioavailability. It is MMF’s advantageous pharmacokinetic properties that lead to enhanced bioavailability, translating into greater activity following ingestion. Without those qualities, MMF might technically still be a prodrug, but it would not be a useful prodrug.

[30] In addition, based on the uses to which MPA had historically been put, namely, treatment of various human conditions and organ transplants in humans, I would also interpret the invention as relating to the use of MMF in humans.

[31] Accordingly, as I construe the ‘285 patent, the utility of the claimed invention (sometimes called the “promise” – see *Pfizer*, above, at para 202) is the enhancement of MPA’s bioavailability through a prodrug – specifically, a mofetil ester of MPA - that has advantageous pharmacokinetic

properties and improved activity over MPA, making it useful for the treatment of a variety of conditions, and as an immunosuppressive agent, in mammals, including humans.

V. Issue One – Was MMF's utility demonstrated or soundly predicted?

[32] Having determined the utility of the claimed invention in the '285 patent, the question is whether that utility had been demonstrated or soundly predicted at the filing date – December 15, 1987. The requirement of utility is met if the invention relates to a "new article, a better article, a cheaper article, or affords the public a useful choice" (C*onsolboard*, above at 521).

(1) Was the utility of MMF demonstrated?

[33] Apotex contends that the '285 Patent does not report any tests of MMF on humans, or any tests of MMF's anti-viral, anti-tumour, or anti-psoriatic effects. Nor were there any specific tests of MMF's alleged pharmacokinetic properties. The data in the patent are limited to MMF's anti-inflammatory activity in female rats, its immunosuppressive and anti-viral activity *in vitro*, and an attempted comparison of a hydrochloride salt of MMF with MPA. I disagree.

[34] The patent sets out a number of examples (Examples 11-15) of *in vitro* and *in vivo* studies demonstrating that MMF reliably delivers MPA. Accordingly, in my view, MMF was shown to have the same beneficial properties as MPA. Its activity is the product of a predictable chemical reaction in which the mofetil ester of MMF is cleaved to yield the active compound MPA. There was no serious dispute among the experts on this point. Dr. Anderson summarized Examples 11-15 as follows:

> [I]n 1987 it was known that the administration of any compound to a mammal including humans which results in the accumulation of MPA in the blood will have the same utility as MPA. It is also my opinion that the data contained in the '285 Patent in fact establish that at the very least administration of MMF to mammals results in accumulation of MPA in the blood. . . Examples 11 to 15 of the '285 Patent also demonstrate the utility of MMF as an immunosuppressive agent, anti-inflammatory agent, anti-tumour agent, anti-viral agent, and anti-psoriatic agents [*sic*] in mammals as stated utility. (para 100)

[35] According to Roche, with this evidence, it has met its obligation to demonstrate the stated utility of the invention as of the filing date. However, having construed the patent as setting out a stated utility beyond that of MPA alone – namely, the advantageous pharmacokinetic properties and improved activity of MMF – I must disagree with Roche's position. I must go on to consider whether that utility was demonstrated or soundly predicted. This question turns on Example 16 of the patent, about which there was considerable dispute between the parties and the experts.

[36] Example 16 was a study conducted on monkeys. MMF and MPA (and another compound of the '285 Patent) were administered to four male monkeys in an oral dosage form. Each of them was treated with one of the compounds, tested, subjected to a wash-out period, and then treated with the next test compound. The data showed that MMF delivered higher concentrations of MPA to the bloodstream (an average concentration of 33.5 µg/mL compared to 6.87 µg/mL) and did so more quickly than MPA on its own (an average time to peak concentration of 1.25 hr compared to 12.9 hr), with equal doses. The relevant data from Example 16 are reproduced below:

Animal ID Nr.	C_{max} (µg/mL)	T_{max} (hr)	$AUC_{0\text{-}24hr}$ (µg/mL · hr)
Mycophenolic acid (MPA)			
A	1.18	24.0	16.8
B	4.24	24.0	41.9
C	12.1	3.0	116.2
D	9.96	0.5	129.3
Mean	6.87	12.9	76.0
±S.D.	±5.04	±12.9	±55.2

Animal ID Nr.	C_{max} (µg/mL)	T_{max} (hr)	$AUC_{0\text{-}24hr}$ (µg/mL · hr)
Mycophenolate mofetil (MMF) hydrochloride			
A	66.2	0.5	136.9
B	18.1	3.0	170.7
C	20.0	0.5	166.9
D	29.5	1.0	243.1
Mean	33.5	1.25	179.4
±S.D.	±22.4	±1.19	±45.1

[37] Apotex raised a number of issues about Example 16, disputing that it serves to demonstrate MMF's advantageous pharmacokinetic properties. Apotex points out that it was not freebase MMF that was administered in the study; the hydrochloride salt of MMF was used. So Example 16 did not constitute a direct comparison with MPA. In addition, Apotex points to the wide inter-subject variability in the study. For example, for some animals, the maximum concentration of the drug was reached at 24 hours (or later), while in another it was reached in 30 minutes. Example 16 was carried out with a small number of subjects which, Apotex contends, diminishes the reliability of the results. Apotex also notes that there is no analysis in the patent showing that the results of Example 16 are statistically significant. The study involved a small sample of subjects and showed a wide variance in results. Without an analysis, a skilled reader would not be satisfied that the results were significant. While Roche contends that the study used a cross-over methodology, which does not require a large sample, Apotex points out that the patent does not specifically state that Example 16 was a cross-over study. In fact, it refers to a "control group", which points away from a cross-over study. There is confusion, therefore, Apotex submits, about the nature of the study and how to read its results.

[38] With respect to the use of a hydrochloride salt, I note that none of the experts made any reference to this in their reports. In cross-examination, most of the expert evidence suggested there

would be no difference between the two forms of MMF once the compounds reached the low pH environment of the stomach. Only a few experts conceded that a salt form of MMF might be more soluble than MMF alone. But there is no concrete evidence before me regarding the respective properties of MMF and its hydrochloride salt. Had this been a significant factor, the experts would likely have noticed it when preparing their affidavits.

[39] The remainder of Apotex's submissions regarding Example 16 collectively amount to an argument that the data generated by it are poor – small sample, variable results, unclear methodology, no statistical analysis. Again, these general criticisms are outweighed by the preponderance of the expert evidence before me. A number of Roche's experts reviewed Example 16 carefully and concluded as follows:

- Example 16 establishes that MMF is absorbed from the gastrointestinal system and converts to MPA in the body. It also shows that MMF produces higher concentrations of MPA in the blood than oral dosing with an equal amount of MPA (Dr. Anderson);

- Example 16 describes a cross-over study designed to compare differences in the compounds' pharmacokinetic parameters. The data show that MMF exhibited an advantageous pharmacokinetic profile over MPA, resulting in greater exposure to MPA in the plasma than when MPA itself is administered orally (Dr. Sawchuk).

- Example 16 shows that MMF has greater bioavailability than MPA. MMF is more efficient at passing from the gastrointestinal tract into the blood system. As such, MMF can be dosed lower, reducing the risk of potential side effects while maintaining therapeutic activity (Dr. Cattral).

- Example 16 is a cross-over study – a scientific methodology that is entirely proper. One can see this from the ID numbers given to the animals and the description of the methodology in the patent. It produced a fair comparison of the respective compounds by using each animal as its own control. The data are reliable and can be used to make sound predictions about relative bioavailability (Dr. Thisted).

[40] I agree with Apotex that the reference to a control group in the description of Example 16 was confusing, and that the data generated by the study showed wide variations. However, I am satisfied that a skilled person would have recognized the methodology as amounting to a cross-over study and that the data would have been interpreted accordingly. I accept Dr. Thisted's uncontradicted conclusion that the data generated by the study are reliable.

[41] Based on this evidence, I find that the stated utility of the invention of the '285 Patent was demonstrated as of the filing date. Based on this evidence, I find that the stated utility of the invention of the '285 Patent was demonstrated as of the filing date. Example 16 shows that MMF has advantageous pharmacokinetic properties that achieve higher concentrations of MPA in the bloodstream at the same dose; ie improved activity. The data show that MMF could serve as an effective prodrug for MPA.

[42] Apotex rightly points out that the patent does not disclose any tests on humans. All of the examples relate to *in vitro* studies or *in vivo* studies in rats and monkeys. But it must be remembered that MMF's sole mission is to deliver MPA, and MPA was well-known to be useful in the treatment of a number of conditions in humans. Therefore, by virtue of its role as an effective prodrug of MPA, which was demonstrated in Example 16, I am satisfied that MMF's utility in humans had also been demonstrated at the relevant date.

(2) Was the utility of MMF soundly predicted?

[43] Even if the stated utility of MMF had not been demonstrated, I am satisfied that it was soundly predicted based on the data in the '285 Patent. A sound prediction is a "*prima facie* reasonable inference of utility" (*Eli Lilly Canada Inc v Novopharm Ltd*, 2010 FCA 197, at para 85).

[44] The factual basis and a line of reasoning supporting a sound prediction of MMF's utility as a delivery mechanism for MPA, plus its advantageous pharmacokinetic properties, are set out in the patent. The examples include data showing that MMF's activity was like MPA's, and that MMF achieved greater bioavailability of MPA at the same dose.

[45] I am satisfied that a skilled person would have understood that an ester derivative of MPA would have the potential of acting as an effective MPA prodrug by virtue of its conversion to MPA on absorption. Ester derivatives were well-known to have this potential and, as will be discussed below, a number of studies of ester derivatives of MPA had been published by the relevant date. None of them had identified a compound that could perform the role of a prodrug. Still, the skilled person would have understood the line of reasoning supporting the assertion that MMF, as an esterified version of MPA, could be used as a prodrug for MPA. And the data in the patent, particularly Example 16, would have demonstrated to the skilled person that the line of reasoning was, indeed, sound.

[46] I find, therefore, that Apotex's allegation that the stated utility of MMF had not been demonstrated or soundly predicted at the filing date is unjustified.

VI. Issue Two – Was MMF obvious?

[47] Apotex maintains that it would have been self-evident to a skilled person that a mofetil ester of MPA would hydrolyze *in vivo* so that some MPA would be present in the plasma, and that MPA would have some activity. In addition, it would have been obvious to the skilled person that the problems with MPA could be solved by means of a prodrug, that an ester prodrug would work given MPA's carboxylic acid group, and that a mofetil ester would have been obvious to try. Further, Apotex argues that the biological effects of MMF were obvious because it is self-evident that the ester would cleave off and leave behind MPA, whose effects were well-known. Again, I disagree.

[48] The test for obviousness was set out by the Supreme Court of Canada in *Apotex Inc v Sanofi-Synthelabo Canada Inc*, 2008 SCC 61 at para 67, and can be re-stated as follows:

(1) Identify the person skilled in the art and the relevant common knowledge;
(2) Identify the inventive concept of the claim in question or if that cannot readily be done, construe it;
(3) Identify what, if any, differences exist between the matter cited as forming part of the state of the art and the inventive concept of the claim or the claim as construed;
(4) Viewed without any knowledge of the alleged invention as claimed, do those differences constitute steps that would have been obvious to the person skilled in the art or do they require a degree of invention?

(1) The Skilled Person and Common General Knowledge

[49] As mentioned, the skilled person for present purposes would have a graduate degree in chemistry, be familiar with medicinal chemistry, drug discovery and formulation, particularly in respect of immunosuppressive agents, and have knowledge of research and treatments relating to autoimmune disorders, psoriasis, inflammatory diseases, tumours and viral infections. The common general knowledge would include familiarity with available immunosuppressive agents, as well as prior art research on potential new compounds, including analogues and prodrugs.

[50] It was certainly well-known in 1987 that prodrugs could be used to overcome a compound's solubility problems. As Dr. Borch pointed out, for drugs that are poorly absorbed one can increase the dose or, "[i]n other cases, the drug may be modified by conversion into a bioreversible derivative (a new chemical compound) that is more readily absorbed than the parent drug, but that reverts to the parent drug after being absorbed. This is known as the prodrug strategy . . ." (para 14). As it was common knowledge that MPA was poorly soluble in water and poorly absorbed *in vivo*, the prodrug strategy would have been something a skilled person would have explored.

[51] In addition, a skilled person would have known that an ester might work since many prodrugs are esters. MPA's carboxylic acid group would have also have suggested use of an ester in the search for a prodrug. In fact, esters of MPA were known to show immunosuppressant, anti-tumour and anti-psoriatic activity (Sweeney, *et al* (1972); Suzuki, *et al* (1976); Ohsugi, *et al* (1976); US Patent 3,868,454). Indeed, the '285 Patent acknowledges this prior art.

[52] However, the prior art also showed that no ester derivative of MPA had better activity than MPA alone. A number of studies showed that esters of MPA had less activity than MPA alone

(Sweeney, *et al* (1972); Suzuki, *et al.* (1976); Suzuki and Mori (1976); Ohsugi, *et al* (1976). As Dr. Sawchuk stated, "the prior art did not teach that one could circumvent the bioavailability problems of MPA by making esters of MPA. Instead the art taught that esters of MPA were not better than MPA, and in most cases, worse" (para 86). Commenting on Suzuki, *et al* (1976) in particular, Dr. Anderson concluded that the "data teach that MPA carboxylic esters show no significant improvement over MPA *in vivo"* (para 80) and would have "taught a person skilled in the art at the relevant date that esterification of the carboxylic acid had no value in improving the activity of MPA or its derivatives in that an increase in water solubility had a negative effect upon activity" (para 82). Dr. Johnson, for Apotex, did not disagree, noting than "none of the ester derivatives of mycophenolic acid possessed greater activity than the parent drug" (para 40). Still, he went on to conclude that a skilled person "would have arrived to the claimed invention of the '285 Patent as a trivial or routine variation on what was already known in January 1987" (para 57).

[53] As for the mofetil ester in particular, it, too, was known in the prior art. A 1954 US patent (2,694,062) contained an example of a mofetil ester prodrug of penicillin, another carboxylic acid. This caused Dr. Roberts to conclude that it was not "surprising, therefore, that mycophenolic acid, a known antibiotic isolated from *Penicillium* broths, could be modified with the same ester as penicillin, also a known antibiotic isolated from *Penicillium* broths. Thus, in my opinion, the mofetil ester of mycophenolic acid represents a compound that would seemingly be trivial and a routine variation to anyone skilled in the art and working in this filed prior to January 1987" (para 80).

[54] Dr. Keana came to a similar conclusion after reviewing some prior art relating to mofetil esters. He referred to a 1983 patent application in the UK relating to mofetil prodrugs of

prostaglandins, a UK patent application relating to niflumic acid, and a 1970 publication (Marchetti and Bergesi) showing that morphethylbutyne is rapidly absorbed and cleaves in the blood and tissues. He finds, based on this prior art, that a skilled person would have made a mofetil ester of MPA "with the confident expectation that the ester would have improved biopharmaceutical properties over those of the parent drug" (para 149).

[55] It should be pointed out that Roche contests some of the prior art on which Apotex relies, noting that there is no evidence showing how this prior art was assembled or that it would be included in the common general knowledge of the skilled person at the time. Prior art should be discoverable on a reasonably diligent search. Without evidence about how it was found, Apotex's submission that the prior it is relying on formed part of the common general knowledge in the field is attenuated. I believe there is reason to be skeptical of the value of some of the prior art references relied on by Apotex's experts, particularly foreign patent applications.

[56] As for the example of niflumic acid cited by Dr. Keana, I note that other experts referred to that compound. Dr. Sawchuk noted that a mofetil ester of niflumic acid actually lowered the parent compound's bioavailability (citing Schiantarelli, *et al*). This prior art did not suggest that a mofetil ester could increase bioavailability; rather, it could stifle the absorption of a well-absorbed drug.

[57] As I view the common general knowledge that would have been within the domain of the skilled person in 1987, I find that he or she would have known that MPA had limited solubility and absorption, that the potential solution might lie in identifying a prodrug, that use of an ester was a possibility, that one of the many esters that could be tried was the mofetil ester.

(2) The Inventive Concept

[58] The inventive concept underlying the ‘285 is well expressed by Dr. Sawchuk: The inventive concept of MMF is the “improved gastric solubility in the stomach and improved delivery of MPA to the general circulation (the bloodstream) compared to when MPA itself is given orally” (para 77). That inventive step was achieved by modifying MPA by adding the mofetil ester.

(3) The Differences

[59] Comparing the inventive concept against the prior art, I find that there was nothing in the prior art showing that use of an ester, even the mofetil ester, would help overcome MPA’s bioavailability problems.

(4) Obvious or a Degree of Invention?

[60] In *Sanofi*, the Supreme Court set out a number of factors to consider at this stage:

- Is it more or less self-evident that what is being tried ought to work? Is there a finite number of identified predictable solutions known to skilled persons?
- What is the extent, nature and amount of effort required? Are routine trials carried out or is the experimentation prolonged and arduous, such that the trials would not be considered routine?
- Is there a motive provided in the prior art to find the solution?
- What was the actual course of conduct that culminated in the invention?

[61] As I view the evidence, it shows merely that there was a possibility that an ester derivative of MPA might deliver enhanced bioavailability. Other potential solutions, such as phenolic esters and analogues, were known and they, too, had been tried without success.

[62] In Apotex's submission, the actual steps taken by the inventors of MMF were not extensive. According to Apotex, the inventors looked at the prior art, including compounds that had already been patented, and composed a list of eight candidates. Two of them were mofetil esters. From there, the inventors merely carried out routine tests to determine that the prodrug would work.

[63] I find that the effort was more extensive than Apotex suggests. Dr. Lee described some of the history. He was part of a team working on immunosuppressive. In the mid-1980s, they were looking at MPA derivatives. At that point, they had researched over a hundred MPA analogues. One of the key areas of interest was solubility in different pH environments. At that point, the lead compound under investigation was known as RS-93004, but it proved unstable and degraded in acidic environments. A successor compound was found – an acetyl solketal ester of MPA - but it, too, proved unstable. Dr. Lee then explored whether a prodrug would provide better solubility and stability. He and a colleague worked from a list of potential esters of MPA. Eight of them were chosen for further testing. A monkey study (Example 16) showed that the mofetil ester had good stability, solubility in the stomach and bioavailability.

[64] Another co-inventor, Dr. Allison, also described his experience in arriving at MMF. He knew about MPA and its potential as an immunosuppressive drug, but he also knew MPA's

limitations due to its poor bioavailability. Dr. Allison also knew that the studies on esters of MPA had failed to show any improvement on MPA's bioavailability. Several hundred analogues and prodrugs had been screened but few were promising. Those that were explored proved unstable. In due course, the mofetil ester of MPA was tried and it looked favourable. A test in monkeys was conducted (Example 16) and the ester was shown to have better bioavailability than MPA. Overall, the process took more than five years.

[65] Clearly, there was a motive to find a solution to MPA's bioavailability constraints, but the prior art was not encouraging. The measures that were taken to find a solution may not have been inventive in themselves, but the inventors showed persistence in continuing to explore a field of inquiry in which the prior art suggested that success was doubtful. Further, the selection of a mofetil ester required a degree of invention on their part. Nowhere in the prior art relating to MPA derivatives was there a signpost pointing to the mofetil. In hindsight, one might identify the mofetil ester of penicillin as the key marker, but all the skilled persons in the field seemed to have passed it by.

[66] In my view, the mofetil ester of MPA was not obvious to try; nor was it more or less self-evident that MMF would work. Simply put, none of the prior art showed that the solubility problems of MPA could be solved by preparing a mofetil ester. I find that Apotex's allegation of obviousness is unjustified.

VII. Conclusion and Disposition

[67] The utility of the claimed invention of the ‘285 Patent, MMF, consists of enhancing MPA’s bioavailability by virtue of its advantageous pharmacokinetic properties and improved activity, making it useful for the treatment of a variety of conditions, and as an immunosuppressive agent, in mammals, including humans.

[68] Apotex alleged that that the utility of MMF had not been demonstrated or soundly predicted at the filing date. However, based on the evidence before me, I find that allegation to be unjustified.

[69] Apotex also alleged that MMF, a mofetil ester of MPA, was an obvious variant on the prior art. However, based on the evidence before me, I find that MMF was not obvious to try. Nor was it more or less self-evident that MMF would work. I also find Apotex’s allegation of obviousness to be unjustified.

[70] Accordingly, Roche has met its burden of proving Apotex’s allegations to be unjustified and I must, therefore, allow this application, with costs.

JUDGMENT

THIS COURT'S JUDGMENT is that

1. The application is allowed, with costs;
2. The Minister of Health is prohibited from issuing a Notice of Compliance to Apotex Inc. until the expiry of Canadian Patent No. 1,333,285.

"James W. O'Reilly"
Judge

Annex “A”

Patent Act, RSC 1985, c P-4

2. In this Act, except as otherwise provided,

“invention” means any new and useful art, process, machine, manufacture or composition of matter, or any new and useful improvement in any art, process, machine, manufacture or composition of matter;

Patented Medicines (Notice of Compliance) Regulations, SOR/93-133

Right of Action

6. (1) A first person may, within 45 days after being served with a notice of allegation under paragraph 5(3)(*a*), apply to a court for an order prohibiting the Minister from issuing a notice of compliance until after the expiration of a patent that is the subject of the notice of allegation.

(2) The court shall make an order pursuant to subsection (1) in respect of a patent that is the subject of one or more allegations if it finds that none of those allegations is justified.

(3) The first person shall, within the 45 days referred to in subsection (1), serve the Minister with proof that an application referred to in that subsection has been made.

(4) Where the first person is not the owner of each patent that is the subject of an application referred to in subsection (1), the owner of each such patent shall be made a party to the application.

(5) Subject to subsection (5.1), in a proceeding in respect of an application under subsection (1), the court may, on the motion of a second person, dismiss the application in whole or in part

Loi sur les brevets, LRC 1985, ch P-4

2. Sauf disposition contraire, les définitions qui suivent s’appliquent à la présente loi.

« invention » Toute réalisation, tout procédé, toute machine, fabrication ou composition de matières, ainsi que tout perfectionnement de l’un d’eux, présentant le caractère de la nouveauté et de l’utilité.

Règlement sur les médicaments brevetés (avis de conformité), DORS/93-133

Droits d’action

6. (1) La première personne peut, au plus tard quarante-cinq jours après avoir reçu signification d’un avis d’allégation aux termes de l’alinéa 5(3)*a*), demander au tribunal de rendre une ordonnance interdisant au ministre de délivrer l’avis de conformité avant l’expiration du brevet en cause.

(2) Le tribunal rend une ordonnance en vertu du paragraphe (1) à l’égard du brevet visé par une ou plusieurs allégations si elle conclut qu’aucune des allégations n’est fondée.

(3) La première personne signifie au ministre, dans la période de 45 jours visée au paragraphe (1), la preuve que la demande visée à ce paragraphe a été faite.

(4) Lorsque la première personne n’est pas le propriétaire de chaque brevet visé dans la demande mentionnée au paragraphe (1), le propriétaire de chaque brevet est une partie à la demande.

(5) Sous réserve du paragraphe (5.1), lors de l’instance relative à la demande visée au paragraphe (1), le tribunal peut, sur requête de la seconde personne, rejeter tout ou partie de la demande si, selon le cas :

(*a*) in respect of those patents that are not eligible for inclusion on the register; or

(*b*) on the ground that it is redundant, scandalous, frivolous or vexatious or is otherwise an abuse of process in respect of one or more patents.

a) les brevets en cause ne sont pas admissibles à l'inscription au registre;

b) il conclut qu'elle est inutile, scandaleuse, frivole ou vexatoire ou constitue autrement, à l'égard d'un ou plusieurs brevets, un abus de procédure.

(5.1) In a proceeding in respect of an application under subsection (1), the court shall not dismiss an application in whole or in part solely on the basis that a patent on a patent list that was submitted before June 17, 2006 is not eligible for inclusion on the register.

(5.1) Lors de l'instance relative à la demande visée au paragraphe (1), le tribunal ne peut rejeter tout ou partie de la demande pour la seule raison qu'un brevet inscrit sur une liste de brevets présentée avant le 17 juin 2006 n'est pas admissible à l'inscription au registre.

(6) For the purposes of an application referred to in subsection (1), if a second person has made an allegation under subparagraph 5(1)(*b*)(iv) or (2)(*b*)(iv) in respect of a patent and the patent was granted for the medicinal ingredient when prepared or produced by the methods or processes of manufacture particularly described and claimed in the patent, or by their obvious chemical equivalents, it shall be considered that the drug proposed to be produced by the second person is, in the absence of proof to the contrary, prepared or produced by those methods or processes.

(6) Aux fins de la demande visée au paragraphe (1), dans le cas où la seconde personne a fait une allégation aux termes des sous-alinéas 5(1)*b*)(iv) ou 5(2)*b*)(iv) à l'égard d'un brevet et que ce brevet a été accordé pour l'ingrédient médicinal préparé ou produit selon les modes ou procédés de fabrication décrits en détail et revendiqués dans le brevet ou selon leurs équivalents chimiques manifestes, la drogue qu'elle projette de produire est, en l'absence d'une preuve contraire, réputée préparée ou produite selon ces modes ou procédés.

(7) On the motion of a first person, the court may, at any time during a proceeding,

(*a*) order a second person to produce any portion of the submission or supplement filed by the second person for a notice of compliance that is relevant to the disposition of the issues in the proceeding and may order that any change made to the portion during the proceeding be produced by the second person as it is made; and

(*b*) order the Minister to verify that any portion produced corresponds fully to the information in the submission or

(7) Sur requête de la première personne, le tribunal peut, au cours de l'instance :

a) ordonner à la seconde personne de produire les extraits pertinents de la présentation ou du supplément qu'elle a déposé pour obtenir un avis de conformité et lui enjoindre de produire sans délai tout changement apporté à ces extraits au cours de l'instance;

b) enjoindre au ministre de vérifier si les extraits produits correspondent fidèlement aux renseignements figurant dans la

supplement.

(8) A document produced under subsection (7) shall be treated confidentially.

(9) In a proceeding in respect of an application under subsection (1), a court may make any order in respect of costs, including on a solicitor-and-client basis, in accordance with the rules of the court.

(10) In addition to any other matter that the court may take into account in making an order as to costs, it may consider the following factors:

(*a*) the diligence with which the parties have pursued the application;

(*b*) the inclusion on the certified patent list of a patent that should not have been included under section 4; and

(*c*) the failure of the first person to keep the patent list up to date in accordance with subsection 4(7).

présentation ou le supplément déposé.

(8) Tout document produit aux termes du paragraphe (7) est considéré comme confidentiel.

(9) Le tribunal peut, au cours de l'instance relative à la demande visée au paragraphe (1), rendre toute ordonnance relative aux dépens, notamment sur une base avocat-client, conformément à ses règles.

(10) Lorsque le tribunal rend une ordonnance relative aux dépens, il peut tenir compte notamment des facteurs suivants :

a) la diligence des parties à poursuivre la demande;

b) l'inscription, sur la liste de brevets qui fait l'objet d'une attestation, de tout brevet qui n'aurait pas dû y être inclus aux termes de l'article 4;

c) le fait que la première personne n'a pas tenu à jour la liste de brevets conformément au paragraphe 4(7).

Annex "B"

EXPERTS & OTHER AFFIDAVIT EVIDENCE

Roche's Evidence

Anthony Allison: Dr. Allison is currently Vice President for Research at Alavita Pharmaceuticals. He is one of the co-inventors of the '285 Patent. In his affidavit he describes the research program on MPA and its derivatives that took place under his co-supervision.

William Lee: Dr. Lee is currently the Senior Vice President Research at Gilead Sciences Inc. He is one of the co-inventors of the '285 Patent. In his affidavit he describes, generally, the work which resulted in the selection and study of MMF as an immunosuppressive agent.

Wayne Anderson: Dr. Anderson is a Professor of Medicinal Chemistry and Pharmaceutical Sciences at the State University of New York (SUNY) at Buffalo, and currently serves as the Dean of the School of Pharmacy and Pharmaceutical Sciences. Dr. Anderson provides opinions with respect to the construction of the '285 Patent as well as the issues of obviousness and utility.

Ronald Sawchuk: Dr. Sawchuk is a Professor of Pharmaceutics at the College of Pharmacy at the University of Minnesota. Dr. Sawchuk provides opinions with respect to the construction of the '285 Patent as well as the issues of obviousness and utility.

Ronald Thisted: Dr. Thisted is a statistician and biostatistician and serves as the Chairman of the Department of Health Studies at the University of Chicago, and the Director of the Biostatistics Core Facility at the University of Chicago Cancer Research Centre. Dr. Thisted's affidavit is limited to a statistical analysis of Example 16 (the monkey study) from the '285 Patent, and in providing rebuttals to the criticisms that Drs. Alloway, Borch and Johnson had of the monkey study data.

Mark Cattral: Dr. Cattral is a physician and surgeon licensed to practice in the Provinces of Ontario and Alberta as well as Illinois and Nebraska in the United States. He is currently a faculty member in the Department of Surgery at the University of Toronto. His opinion is limited to the use and impact of medications to address organ rejection in transplant patients, and to comments on what is to be learned from the various tests and data found in the '285 Patent.

Apotex's Evidence

Irving Johnson: Dr. Johnson is a well-published author with over 50 years of experience in the pharmaceutical industry. He has also been recognized with numerous awards. Dr. Johnson provides opinions with respect to the construction of the '285 Patent as well as the issues of obviousness and utility.

Richard Borch: Dr. Borch is a Professor of Medicinal Chemistry and Molecular Pharmacology at Purdue University. In his affidavit he provides opinions with respect to the construction of the '285 Patent as well as the issues of obviousness and utility.

John Keana: Dr. Keana is a Professor Emeritus in the Department of Chemistry at the University of Oregon. In his affidavit he provides an opinion on whether the subject matter of the ‘285 Patent would have been obvious prior to 30 January 1987.

Edward Roberts: Dr. Roberts is currently a Professor of Translational Chemistry and Medicine at the Scripps Research Institute. In his affidavit Dr. Roberts provides opinions with respect to the construction of the ‘285 Patent as well as the issues of obviousness and utility.

Rita Alloway: Dr. Alloway is currently a Research Professor in the Department of Internal Medicine at the University of Cincinnati specializing in transplantation and immunosuppressive drug regimens. In her affidavit Dr. Alloway provides opinions with respect to the construction of the ‘285 Patent as well as the issue of utility.

FEDERAL COURT

SOLICITORS OF RECORD

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No one appearing	FOR THE RESPONDENT – Minister of Health

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