Federal Court  Cour fédérale

Date: 20140613

Docket: T-1151-12

Citation: 2014 FC 567

Ottawa, Ontario, June 13, 2014

PRESENT: The Honourable Mr. Justice O'Reilly

BETWEEN:

ALLERGAN INC AND ALLERGAN, INC

Applicants

and

THE MINISTER OF HEALTH
AND APOTEX INC

Respondents

JUDGMENT AND REASONS

I. Overview

[1] The applicants, Allergan, ask me to issue an order prohibiting the Minister of Health from issuing a notice of compliance (NOC) to Apotex Inc, relying on s 6(1) of the *Patented Medicines (Notice of Compliance) Regulations*, SOR/93-133 (see Annex A for all enactments cited). The NOC would enable Apotex to market a generic version of a product protected by Allergan's Canadian Patent No 2,585,691 (the '691 patent). The '691 patent relates to eye drops used in the

treatment of glaucoma and ocular hypertension. Allergan calls its product "LUMIGAN RC". In these reasons, for ease of reference, I will call this product "new Lumigan". The '691 patent issued in 2009 and will not expire until 2026.

[2] Apotex has alleged that Allergan's patent is invalid on the grounds of obviousness, lack of utility, and anticipation and, therefore, that Apotex should be entitled to an NOC for an equivalent generic product. Allergan maintains that Apotex's allegations are unjustified and that the Minister should be prohibited from granting Apotex its NOC.

[3] I agree with Allergan that Apotex's allegations of obviousness, lack of utility, and anticipation are unjustified. Therefore, I must allow Allergan's application.

[4] There are three issues:

1. Is the subject matter of the '691 patent obvious?
2. Could the stated utility of the '691 patent be soundly predicted?
3. Was the '691 patent anticipated?

II. The '691 Patent

[5] Allergan previously owned a patent for formulations of ocular products with the same purpose as, and similar ingredients to, new Lumigan (Canadian Patent No 2,144,967 – the '967 patent). The '967 patent, which expired in 2013, covered a wide range of concentrations of active ingredients and preservatives and included within that range a product containing .03% bimatoprost (Bp) and 50 parts per million (ppm) benzalkonium chloride (BAK), as the

preservative. Allergan marketed that product as “LUMIGAN”, to which I will refer as “old Lumigan”.

[6] Old Lumigan caused some dose-dependent side effects, particularly an eye irritation called “hyperemia.” Allergan sought to create a product with fewer adverse reactions. It arrived at the formulation for new Lumigan, which contained only a third of the Bp contained in old Lumigan, but used four times as much BAK. Based on its studies of this revised formulation, Allergan believed that patients using new Lumigan would likely enjoy a comparable reduction of intraocular pressure (IOP) with fewer side effects than with old Lumigan.

[7] The ‘691 patent is entitled “Enhanced Bimatoprost Ophthalmic Solution”. It makes reference to the prior art and includes data relating to the testing of various concentrations of Bp (and other active ingredients) and BAK (and other preservatives). In particular, it mentions old Lumigan containing .03% Bp and 50 ppm BAK, as well as other products using BAK as a preservative in concentrations of 150 to 200 ppm.

[8] The ‘691 patent relates to a formulation for eye drops primarily for use in treating glaucoma. The formulation contains a single active ingredient, Bp, in a concentration of between .005% and .02%. The other main ingredient is BAK at concentrations from 100 to 200 ppm. While BAK acts primarily as a preservative, it has other properties, too, as will be discussed below. Claim 16 of the ‘691 patent falls within this formulation. It claims a combination of .01% Bp and 200 ppm of BAK. Claim 19 claims the use of this formulation in the treatment of glaucoma or intraocular hypertension. These are the only claims in issue here.

[9] The patent lists various embodiments of the invention ranging from .01% to .02% Bp, all with 200 ppm BAK. In terms of data, the patent contains two graphs (Examples 2 and 4). The first shows the results of an *in vivo* test in rabbits of .03% Bp with 50 ppm BAK (*ie*, old Lumigan) compared with .03% Bp with 200 ppm BAK. Other data were provided, but they are not relevant here. The results showed that use of BAK at 200 ppm increased by 57% the concentration of Bp in the aqueous humour of the rabbits' eyes.

[10] The second graph provides the results of an *in vitro* study in rabbit corneal epithelial cell layers of two concentrations of Bp (.015% and .03%) combined with various concentrations of BAK (from 50 ppm to 200 ppm). None of the combinations corresponds with new Lumigan (*ie*, .01% Bp with 200 ppm BAK). However, .015 Bp was tested both with 50 ppm and 200 ppm BAK. The results showed that the use of the higher amount of BAK achieved greater penetration of Bp across the corneal cells.

[11] The patent also describes a treatment scenario in which a product with a fairly low concentration of Bp (.015%) and a relatively high amount of BAK (125 ppm) – which is obviously not new Lumigan – would achieve a greater lowering of IOP and less hyperemia than old Lumigan. No such test was ever conducted.

III. Construction of the ‘691 Patent

[12] Generally speaking, the patent must be construed through the eyes of the person skilled in the relevant art. Here, the parties agree that this notional person would have the skills of a formulator experienced in creating optical formulations and those of an ophthalmologist experienced in treating glaucoma.

[13] In my view, the claims in issue are clear. Claim 16 relates to a product with lower Bp (.01%) and higher BAK (200 ppm) than old Lumigan (which had .03% and 50 ppm, respectively). Claim 19 relates to the use of that product for treating glaucoma in humans. Since they are unambiguous, I need not resort to the patent’s specification to construe them. However, the specification helps explain the inventive concept of the patent and describes the utility of the invention, which forms part of the analysis of obviousness and sound prediction below.

IV. Issue One – Is the subject matter of the ‘691 patent obvious?

[14] The parties agree that Supreme Court of Canada laid out the test for obviousness in *Apotex v Sanofi-Synthelabo Canada Inc*, 2008 SCC 61, at para 67 [*Sanofi*]. I will address each element of the test, as follows.

A. *Identify the skilled person to whom the patent is addressed*

[15] As mentioned, the parties accept that the relevant person would have the skills of an optical formulator and an ophthalmologist experienced in treating glaucoma.

[16] Both parties provided expert opinions on the scope of the ‘691 patent. Allergan relied on the opinions of Dr Valentino Stella and Dr Harry Quigley. Apotex relied on Dr Anthony Palmieri, Dr Arthur Kibbe, and Dr Ian Grierson. The experts’ credentials are summarized in Annex B.

B. *Identify the state of the art*

[17] The relevant date for this assessment is that on which the ‘691 patent was filed – March 16, 2005. At that time, the experts all agree that Bp was a compound known to be useful for lowering IOP, and BAK was a well-known preservative. Bp was the active ingredient (at .03%) in old Lumigan, which had 50 ppm BAK.

[18] The skilled person would likely have viewed a reduction of Bp by one third to .01% in new Lumigan to cause a corresponding diminution of efficacy in lowering IOP. Still, .01% Bp would likely still have some efficacy. A 2001 study showed that .03% Bp was more effective than .01% Bp.

[19] However, he or she would also have regarded a reduction of Bp as causing fewer side effects. Bp causes dose-dependent eye hyperemia. Therefore, reducing the dose of Bp would correspondingly reduce hyperemia.

[20] The skilled person would likely have been concerned about the increase of BAK to 200 ppm because of its cytotoxicity. While optical formulations containing that amount of BAK were known, tolerated by patients, and on the market, a skilled person would likely have regarded a

substantial increase in the concentration of BAK as a negative factor. Since 50 ppm of BAK was sufficient to achieve a preservative effect in old Lumigan, there was no obvious reason to increase its concentration.

C. *Identify the inventive concept of the claims*

[21] The parties differ on the meaning of "inventive concept". Allergan argues that the inventive concept is different from the claimed invention which, in turn, is different from the stated utility of the claimed invention. On the question of obviousness, then, the inventive concept of the '691 patent, according to Allergan, is the creation of a new formulation (new Lumigan) that achieves a comparable effect to that of old Lumigan, but with less Bp.

[22] However, on the question of construction of the claims, Allergan argues that there is no specific indication (or "promise") that the claimed invention will have any particular effect in lowering IOP. The claimed invention is simply an ocular formulation with .01% Bp and 200 ppm BAK.

[23] Apotex maintains that the patent should be given only one interpretation for all purposes – infringement, obviousness, and utility. Therefore, as Allergan suggests, the claimed invention is a formulation with .01% Bp with 200 ppm BAK and that, too, is the definition of the invention that should be applied to all grounds of alleged invalidity, including obviousness. Accordingly, Apotex argues that altering the amounts of Bp and BAK was an obvious modification of old Lumigan.

[24] In my view, the interpretation of the patent should be as consistent as possible across the various issues in play. A patentee should not, for example, be able to "read up the invention for obviousness and read it down for utility" (*Hoffmann-La Roche v Apotex*, 2011 FC 875, at para 22). To do so would be unfairly advantageous for a patent holder who might wish to assert that its invention was an unforeseeable innovation (and, therefore, not obvious) and, at the same time, contend that the invention's useful properties could be readily inferred (and, therefore, soundly predictable).

[25] However, that does not mean that construction of the claims necessarily determines the inventive concept for purposes of the obviousness analysis. Claims construction is an important preliminary exercise particularly where infringement is in issue. One has to know what the parameters of the claimed invention are in order to determine whether another party has encroached on them. Identifying the inventive concept is a separate exercise forming part of the analysis of whether the patent claims something that is truly inventive, and therefore not obvious. Where the patent relates to a bare chemical formula, the court must refer to the claim and the specification to determine what the claim's inventive concept is (*Sanofi*, above, at 67, 77). I believe the same should be true, as here, where the claim relates to a bare list of ingredients.

[26] In my view, reading the '691 patent as a whole, the inventive concept of Claims 16 and 19 is a formulation with reduced Bp but with comparable efficacy to old Lumigan, achieved by increasing BAK.

[27] As discussed above, the data in the patent show that BAK had penetration enhancing properties, in addition to its known preservative qualities. Even though there was no data for the precise formulation identified in Claim 16, a skilled reader of the patent would see that raising BAK to 200 ppm caused a significant increase in the penetration of Bp. The closest data showed that a formulation with .015 Bp and 200 ppm BAK achieved substantially greater permeability across rabbit cell layers than a .015% BP and 50 ppm BAK formulation. In fact, the results for .015% Bp and 200 ppm BAK were higher than for .03% Bp and 50 ppm BAK (*ie*, old Lumigan). Similarly, increasing BAK from 50 ppm to 200 ppm in a .03% Bp formulation caused a substantial rise in the concentration of Bp in rabbit eyes.

[28] From this data, it appears to me that a conclusion about the efficacy of a .01% Bp-200 ppm BAK solution would involve no more than a simple extrapolation from the data regarding other combinations. Since .015% Bp with 200 ppm BAK achieved greater effect than old Lumigan, reducing Bp further to .01% would likely result in values more or less comparable to old Lumigan. In other words, new Lumigan would likely cause roughly equivalent IOP lowering to old Lumigan.

[29] As will be seen below in the discussion of sound prediction, this interpretation of the data in the ‘691 patent is supported by expert opinion.

D. *Identify any differences between the state of the art and the inventive concept*

[30] Apotex argues that combinations of Bp and BAK for use in treating glaucoma were included in the ‘967 patent, mentioned above. In addition, old Lumigan itself represented such a

combination. Further, it was known that Bp could be effective at low concentrations (even as low as .003%), so a skilled person would expect that using Bp at .01% would lower IOP, at least to some extent. Accordingly, there is no difference between the inventive concept of the claims in issue and the state of the art.

[31] I have already found the inventive concept to be a formulation with a fairly low concentration of Bp (.01%) that has a comparable effect in lowering IOP to old Lumigan (at .03%), due to the penetration enhancing effect of 200 ppm BAK. Nothing in the state of the art suggested such a possibility.

[32] As mentioned, according to the state of the art, to reduce Bp would be to reduce efficacy. Increasing BAK could be contrary to the accepted wisdom that BAK had its own side effects and, therefore, that its use should be minimized or eliminated, not increased. Further, there was nothing in the literature that pointed to BAK being a penetration enhancer for a compound like Bp. Dr Stella noted that studies showed that BAK might act as a penetration enhancer for some compounds but not for a relatively lipophilic molecule like Bp.

E. *Do those differences constitute steps that would have been obvious to the skilled person?*

[33] Apotex submits that the inventive concept of the claims in issue corresponds with the state of the art and, therefore, the claimed formulation was obvious. Accordingly, in Apotex's submission a skilled person would have known that the combination of .01% and 200 ppm BAK was possible and would cause lowering of IOP.

[34] In my view, as described above, there are significant differences between the inventive concept of the claims in issue and the state of the art at the relevant time. Those differences would not have been obvious to the skilled person. The formulation of new Lumigan with efficacy comparable to old Lumigan required experimentation (as seen in the patent itself) and inventive steps, such as the trial of various combinations of Bp and BAK (and other ingredients).

[35] The evidence shows that Allergan conducted numerous tests before arriving at the claimed invention. The company spent millions of dollars and devoted thousands of person-hours to the project. The result was a commercially successful product. Clearly, it was not self-evident that the claimed formulation would work as it did. In my view, that formulation was not obvious to try.

[36] Accordingly, Apotex's allegation that the subject matter of the '691 patent was obvious is not justified.

V. Issue Two – Could the stated utility of the '691 patent be soundly predicted?

[37] On my reading of the patent, the stated utility of the claims in issue is that new Lumigan would have a comparable effect to old Lumigan, with less Bp (and, therefore, fewer side effects). That utility had not actually been demonstrated as the data in the patent did not relate directly to the claimed formulation – .01% Bp with 200 ppm BAK. Therefore, the question here is whether it could have been soundly predicted that new Lumigan was likely to cause a comparable lowering of IOP compared to old Lumigan, given its substantial reduction of Bp and significant increase in BAK.

[38] Apotex maintains that the data set out in the ‘691 patent do not provide a basis for a sound prediction of the stated utility, namely, a comparable effect in lowering IOP to that of old Lumigan. In addition, the patent does not set out the line of reasoning that would link that data to the stated utility. For example, the patent makes no connection between the two primary data sets (the *in vitro* and *in vivo* studies) that would enable a skilled person to arrive at a prediction about the utility of the invention.

[39] A patent will be valid based on a sound prediction of utility where it sets out a factual basis for the prediction and a sound line of reasoning connecting the facts and the predicted utility (*Apotex Inc v Wellcome Foundation Ltd*, 2002 SCC 77, at para 70). In my view, both a factual basis and a sound line of reasoning are set out in the ‘691 patent.

[40] The factual basis consists of the data described above. The sound line of reasoning is implicit in the data itself and would be apparent to the skilled reader; it did not have to be explicitly laid out.

[41] The data clearly showed that BAK had a penetration enhancement effect, so that a relatively low dose of Bp (.01%) combined with a relatively high dose of BAK (200 ppm), would reduce IOP comparably to old Lumigan. The skilled person would be able to interpret the data easily to arrive at that prediction.

[42] On this question, I am persuaded by the reasoning of Dr Stella, who stated:

> Taken together, the experiments disclosed in the ‘691 Patent also taught the skilled formulator that the concentration of bimatoprost could be

> reduced from the previously marketed concentration of 0.03% and still yield a formulation that achieved a similar aqueous humor concentration of bimatoprost. The *in vitro* data showed that the apparent permeability across rabbit corneal epithelial cell layers increased with increasing concentrations of BAK from 0.005% (50 ppm) to 0.02% (200 ppm) for a formulation with 0.015% bimatoprost. From Figure 2 of the '691 Patent, in comparing the second and fourth bars (from the left), the apparent permeability increased by approximately 3x when 200 ppm BAK was present instead of 50 ppm BAK. This provides useful, relative data that the skilled formulator would use to predict that a lower concentration of bimatoprost would be sufficient to achieve a similar aqueous humor concentration.
>
> Specifically, the composition of claim 16 contains 0.01% bimatoprost and 0.02% (200 ppm) BAK. Because the concentration of bimatoprost is reduced the skilled formulator would ordinarily expect that the aqueous humor concentration of bimatoprost would be similarly reduced. However, because the effect of increasing BAK on increasing permeability has been demonstrated with the *in vivo* data from Example 2, and supported by the *in vitro* data from Example 4, the skilled formulator would have soundly predicted that the four-fold increase in BAK concentration (from LUMIGAN® 0.03%) would permit a 2/3 reduction in bimatoprost concentration (from LUMIGAN® 0.03%) and still achieve a similar aqueous humor concentration.
>
> Therefore, based on the disclosure of the '691 Patent, the skilled formulator would have had a factual basis for soundly predicting that the formulation claimed in Claim 16 would achieve superior corneal penetration and thus yield comparable aqueous humor levels as the old LUMIGAN® 0.03% formulation in humans.

[43] Apotex asserts that the rabbit model used in the '691 patent was not suitable for making predictions about the effect in humans. Indeed, the inventors were not sure whether the effects seen in the rabbit eye would translate to the human eye. Further, the Bp administered to the rabbits was the parent molecule, not the Bp acid that is active in lowering IOP; the parent molecule is less lipophilic and more likely, therefore, to be amenable to BAK's penetration enhancing qualities. Finally, Apotex maintains that there is no basis for connecting the results of the *in vivo* and the *in vitro* tests.

[44] I am satisfied that all of these concerns were answered by Allergan's experts, as follows:

- The rabbit model is reliable and commonly used for studying ophthalmic drugs. While there are differences between rabbit eyes and human eyes, they do not prevent skilled persons from reaching valid conclusions. (Dr Stella and Dr Quigley).

- The protocol for Example 2, in which the inventors measured the concentration of bimatoprost acid in the eye, was proper in order to determine the IOP lowering effect. (Dr Quigley).

- Taken together, the *in vitro* and *in vivo* studies showed that the inventors had achieved satisfactory (or equivalent) penetration of bimatoprost through the epithelial cell layer, and a satisfactory (or equivalent) concentration of bimatoprost in the aqueous humor to that achieved by higher concentrations of bimatoprost and lower concentrations of BAK. (Dr Quigley).

- While the skilled formulator would not have been able to calculate the *in vivo* efficacy based on the *in vitro* study, there is enough information in Examples 1-4 of the patent to make a sound prediction that the formulations, particularly claim 16, would deliver a comparable bimatoprost aqueous humor concentration as old Lumigan. (Dr Stella).

[45] Accordingly, I am satisfied that the stated utility of the claims in issue was soundly predicted based on the factual evidence and the line of reasoning set out in the '691 patent. Apotex's allegation to the contrary is not justified.

VI. Issue Three – Was the '691 patent anticipated by the '967 patent?

[46] Apotex argues that the claims in issue are anticipated by the '967 patent. It is clear that the '967 disclosed active ingredients, including Bp, that could be combined with preservatives, including BAK, in amounts that would include the formulation of new Lumigan. Further, the formulations disclosed in the '967 could be used to treat glaucoma.

[47] However, on the evidence here, the formulation in Claim 16, new Lumigan, has the special advantage of lowering IOP effectively while using a fraction of the active ingredient usually required for a similar result. This advantage benefits patients who experience hyperemia with use of the .03% Bp formulation of old Lumigan.

[48] Assuming that Apotex's characterization of the '691 patent is accurate – that is, that it is a selection patent – I note the following from *Sanofi*:

> If in reading the genus patent the special advantages of the invention of the selection patent are not disclosed, the genus patent does not anticipate the selection patent (at para 33).

[49] Therefore, since the special advantage of new Lumigan was not disclosed, the '967 patent does not anticipate claims 16 and 19 of the '691 patent.

[50] Even if there had been disclosure, I am not satisfied that there had been enablement. As discussed above, Lumigan took inventive steps to achieve the formulation of Claim 16. Where "an inventive step was required to get to the invention of the second patent, the specification of the first patent will not have provided enabling disclosure" (*Sanofi*, at para 33).

[51] Therefore, Apotex's allegation of anticipation is not justified.

VII. Conclusion and Disposition

[52] Allergan has met its burden of showing that Apotex's allegations of invalidity are unjustified. Therefore, I will grant an order prohibiting the Minister of Health from issuing an NOC to Apotex for its generic version of LUMIGAN RC® until the expiry of the '691 patent.

JUDGMENT

THIS COURT'S JUDGMENT is that:

1. The application is allowed, with costs.

2. The Minister of Health is prohibited from issuing an NOC to Apotex for its generic version of LUMIGAN RC® until the expiry of the '691 patent.

"James W. O'Reilly"
Judge

Annex “A”

Patented Medicines(Notice of Compliance) Regulations, SOR/93-133	*Règlement sur les médicaments brevetés (avis de conformité),* DORS/93-133
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.	**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.

Annex "B"
EXPERTS

Allergan's Expert Witnesses

Dr Valentino Stella is a Distinguished Professor of Pharmaceutical Chemistry at the University of Kansas. He addresses Apotex's allegations and interprets the '691 Patent from the perspective of the formulator.

Dr Harry Quigley is a clinical and research ophthalmologist, as well as a Professor of Ophthalmology at John Hopkins University in Maryland. He addresses Apotex's allegations and interprets the '691 Patent from the perspective of the ophthalmologist.

Apotex's Expert Witnesses

Dr Kibbe is a distinguished Professor of Pharmaceutical science and has been teaching formulation design to graduate students since the 1970s. He has prepared ophthalmic formulations, worked in drug development for both pharmaceutical companies and pharmaceutical regulators and has edited and published chapters in leading textbooks on pharmaceutical formulations.

Dr Palmieri has a Ph D in Pharmaceutics, is a professor of Pharmacy and has taught all aspects of formulation development, including ophthalmic solution design, to graduate and undergraduate students.

Dr Grierson is a distinguished Professor of Ophthalmology at the University of Liverpool. Since 1980, he has consulted for drug companies on glaucoma research including advising on the effects of excipients and drugs when applied to the eye.

FEDERAL COURT

SOLICITORS OF RECORD

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