Federal Court  Cour fédérale

20111117

Docket: T-154-10

Citation: 2011 FC 1316

Ottawa, Ontario, November 17, 2011

PRESENT: The Honourable Mr. Justice Crampton

BETWEEN:

**ALLERGAN INC., ALLERGAN SALES INC.
AND ALLERGAN, INC.**

Applicants

and

**THE MINISTER OF HEALTH
AND SANDOZ CANADA INC.**

Respondents

REASONS FOR JUDGMENT AND JUDGMENT

[1] The Applicants, (collectively "Allergan"), seek an order pursuant to subsection 6(1) of the *Patented Medicines (Notice of Compliance) Regulations*, SOR/93-133 to prevent the Minister of Health from issuing a Notice of Compliance (NOC) to Sandoz Canada Inc. until the expiry of two patents that Allergan owns, namely, Canadian Patent No. 2,440,764 (the '764 Patent) and Canadian Patent No. 2,225,626 (the '626 Patent).

[2] If issued, the NOC that Sandoz has requested would permit it to market in Canada a generic version of a drug which combines two active ingredients, brimonidine tartrate (0.2%) ("brimonidine") and timolol maleate (0.5%) ("timolol"), used in the treatment of glaucoma. Allergan currently markets the branded version of that drug under the name "COMBIGAN".

[3] In support of its NOC, Sandoz filed an abbreviated new drug submission with the Minister in which it compared its drug (the "Generic Drug") to COMBIGAN. Sandoz then sent a Notice of Allegation (NOA) to Allergan in which it alleged, among other things, that:

i. the invention claimed by the '764 Patent was obvious as of the priority date of April 19, 2002 (the "Priority Date"), such that the '764 Patent is invalid;

ii. the Product Monograph of the Generic Drug will not induce infringement of any of the claims in the '626 Patent;

iii. the Generic Drug will not infringe any of the claims in the '626 Patent; and

iv. the '626 Patent is invalid for inutility, on the basis that:

(a) the claims therein cover non-useful subject matter; and

(b) the utility of that subject matter could not be soundly predicted as of the Priority Date and the Canadian filing date of the '626 Patent.

[4] Allergan submits that Sandoz's allegations are not justified, as contemplated by subsection 6(2) of the Regulations. That said, Allergan concedes that Sandoz has put the invalidity issues raised in its NOA "into play", such that the presumption of validity of the '764 Patent and the '626 Patent has been rebutted (*Novo Nordisk Canada Inc v Cobalt Pharmaceuticals Inc*, 2010 FC 746, at paras

68-69 [*Novo Nordisk*]; *Pfizer Canada Inc v Novopharm Ltd*, 2009 FC 638, at paras 35-36 [*Pfizer* (2009 FC 638)]).

[5] To obtain the order of prohibition that it seeks in this application, Allergan must demonstrate, on the balance of probabilities, that Sandoz's allegations are not justified, either with respect to:

i. the alleged obviousness of the invention claimed by the '764 Patent; or

ii. all of the above-mentioned allegations that have been made in respect of the '626 Patent.

[6] For the reasons that follow, I have concluded that Allergan has met its burden in respect of the alleged obviousness of the invention claimed by the '764 Patent. Therefore, I will issue the requested order of prohibition in respect of the '764 Patent.

[7] Given that the '764 Patent was issued more recently than the '626 Patent, it is not strictly necessary, for the purposes of the present application, to consider the allegations that Sandoz has made in respect of the '626 Patent. In brief, any determinations that may be made in respect of the latter patent cannot affect the period of time during which Sandoz will be unable to market the Generic Drug, due to the conclusion I have reached in respect of the '764 Patent.

[8] Nevertheless, in the event that I am found to have erred in my conclusion that the subject matter of the '764 Patent was not obvious, I have also assessed the issues that have been raised in respect of the '626 Patent. In this regard, the issue of inducement of infringement is determinative, because the '626 Patent is a use patent, which cannot be directly infringed by Sandoz. I have

concluded that Allergan has not met its burden on this issue. In other words, I have determined that Sandoz's allegation that it will not induce infringement of the '626 Patent is justified.

[9] In the event that my conclusion on the inducement issue is overturned, I have proceeded to address the various other allegations that Sandoz has made in support of its position that the Generic Drug will not infringe the '626 Patent and that the '626 Patent is invalid. I have concluded that Allergan has demonstrated, on a balance of probabilities, that those allegations are not justified.

[10] In short, for the reasons that follow, I have determined that this application will be allowed with respect to the '764 Patent but dismissed with respect to the '626 Patent.

I. Background

A. *Glaucoma*

[11] Glaucoma is a chronic disease of the optic nerve that leads to progressive, irreversible loss of vision and can lead to blindness.

[12] The precise cause of damage to the optic nerve is not entirely understood. However, it is often, but not always, associated with increased pressure of the aqueous humor located at the front of the eye. This is usually referred to as increased intraocular pressure (IOP), or ocular hypertension. If left untreated, IOP can lead to the development of glaucoma. It is for this reason, and the fact that IOP lowering drugs seem to prevent further progression of the disease, that IOP is widely considered to be a major risk factor for glaucoma.

[13] The terms "elevated IOP" and glaucoma were once used synonymously. However, it appears that it is now understood that glaucoma is a complicated disease which may be associated with high IOP, but can also strike people with statistically normal IOP.

[14] Although there is no cure for glaucoma, several different types of drugs have been developed for its treatment. For more than 100 years, ophthalmologists have been using cholinergic drugs to treat glaucoma and IOP. Drugs in this class mimic and amplify the parasympathetic nervous system, and have the general effect of relaxing muscle tissue. However, they have been associated with significant side effects.

[15] A second class of drugs that have been used since at least the 1920s to treat glaucoma are andrenergic agents, such as epinephrine. With the advent of modern anti-glaucoma drugs beginning in the 1970s, the use of epinephrine has become progressively less popular, mainly due to its significant side effects.

[16] A third class of drugs that are used to lower IOP and treat glaucoma are best known as beta andrenergic antagonists, or beta (ß) blockers. Beta andrenergic antagonists block natural epinephrine from having activity at the ß-receptors, and are thereby thought to allow the same IOP lowering effects as epinephrine, but with fewer side effects. In addition, beta blockers reduce IOP by decreasing aqueous humor production. Beta blockers are one of the most commonly used classes of drugs for treating glaucoma, and include drugs such as timolol, which was first made available commercially by Merck Frosst Canada Ltd. in approximately 1978, under the brand name TIMOPTIC. Since that time, timolol has become one of the mainstays in the treatment of glaucoma and IOP.

[17] A fourth class of IOP lowering drugs is comprised of drugs generally known as alpha-2 agonists. Alpha-2 agonists act by stimulating the alpha andrenergic receptors, thereby lowering IOP. Drugs in this class first became commercially available in the 1980s. Brimonidine is a drug in this

class that has been available as an ophthalmic solution since approximately 1996, when Allergan launched a product containing 0.2% by weight of brimonidine, under the brand name ALPHAGAN. Sandoz launched a generic version of ALPHAGAN the following year, after sending an NOA to Allergan which was not challenged.

[18] Two additional classes of IOP lowering drugs are prostaglandin analogs, such as latanoprost, and carbonic anhydrase inhibitors (CAIs), such as dorzolamide and brinzolamide.

[19] While both brimonidine and timolol can be effective in reducing IOP in some patients, monotherapy involving these medications does not help everyone. For example, these drugs may not be considered to be useful for certain patients because of their undesirable side effects or their medical contraindications, or because they are not effective for a particular individual. In other patients, additional IOP lowering beyond the level that can be achieved with either of these drugs administered separately is required. Accordingly, those two drugs began to be prescribed for concomitant (also known as adjunctive or serial) administration prior to the filing date of the ‘764 Patent.

B. *The Relevant patents*

[20] Pursuant to section 4 of the Regulations, Allergan listed four patents in the Patent Register in respect of COMBIGAN. However, Allergan has chosen to bring this application only in respect of the allegations that Sandoz has made regarding the ‘764 Patent and the ‘626 Patent.

[21] The ‘764 Patent was filed on April 9, 2003, published on October 19, 2003 and issued on October 25, 2005. It claims priority from a U.S. Patent filed on April 19, 2002.

[22] The ‘764 Patent makes claims with respect to ophthalmic topical pharmaceutical compositions for the treatment of glaucoma or ocular hypertension including, among other things, a composition comprising brimonidine (0.2%), timolol (0.5%) and the preservative benzalkonium chloride (BAK) (0.001% to 0.01%) in a pharmaceutically acceptable carrier. The descriptive section of that patent concludes by stating that, when administered twice a day (BID) for three months, this combination of brimonidine and timolol was superior to equivalent concentrations of timolol administered BID and brimonidine administered three times a day (TID), in lowering the elevated IOP of patients with glaucoma or ocular hypertension. It also states that the combination “administered BID demonstrated a favorable safety profile that was comparable to Timolol BID and better than Brimonidine TID with regard to the incidence of adverse events and discontinuation due to adverse events.”

[23] The ‘626 Patent was filed on June 17, 1996, published on January 16, 1997, issued on September 3, 2002 and claims priority from U.S. Patent filed on June 28, 1995.

[24] The ‘626 Patent describes a “new method of protecting the optic nerve and retina of the mammalian eye from damage by glaucoma and other noxious provocations.” This neuroprotection is stated to be provided by a new use of an effective amount of certain compounds, including brimonidine, “to inhibit or prevent nerve cell injury or death … for protecting the retinal or optic nerve cells in a mammal suffering a noxious action or at risk of experiencing a noxious action on said nerve cells.” Prior to the Priority Date, brimonidine had been known to be effective at lowering IOP and was widely used for that purpose.

C. *COMBIGAN*

[25] COMBIGAN is the brand name of the composition described in the '764 Patent. It is sold in Canada pursuant to NOCs issued to Allergan on December 9, 2003 (for the control of IOP) and August 24, 2007 (for the reduction in long term fluctuation of IOP). As is the case with the Generic Drug, the active ingredients in COMBIGAN are brimonidine (0.2%) and timolol (0.5%), and the preservative is BAK (0.005%).

II. The Parties' Experts

[26] Three individuals adduced expert evidence on behalf of Allergan and two adduced such evidence on behalf of Sandoz.

A. *Allergan's experts*

[27] Mr. Gary J. Beck is one of the inventors of COMBIGAN identified in the '764 Patent. From 1995 to 1999, he held the title of Scientist at Allergan. In that capacity he had responsibility for, among other things, attempting to develop an ophthalmic formulation that combined brimonidine and timolol. In 1999, he became a Global Project Manager and thus remained closely involved in the development of the combination product. He was also part of the team that prepared and submitted the successful application for approval of COMBIGAN to the U.S. Food and Drug Administration (U.S. FDA). Mr. Beck provided affidavit evidence and was cross-examined with respect to the development of COMBIGAN, its reduced side effects relative to brimonidine monotherapy and timolol monotherapy, its efficacy, its commercial success and its development costs.

[28] Dr. Robert Fechtner is a Professor of Ophthalmology and Director of the Glaucoma Division at the New Jersey Medical School of the University of Medicine and Dentistry of New

Jersey. He is also an attending physician at University Hospital in Newark, New Jersey and conducts his clinical practice at the New Jersey Medical School, where he has studied and treated patients with glaucoma. In addition being on various boards and committees related to glaucoma, he has served on many editorial boards for publications in the field of ophthalmology. His main research focus during his career has been the treatment of glaucoma. He has authored many articles, books and chapters related to glaucoma and the reduction of IOP. Dr. Fechtner provided affidavit evidence with respect to the subject matter of the '764 Patent, the person of ordinary skill in the art ("POSITA") to which that patent relates, Sandoz's NOA and the evidence provided by Sandoz's experts, particularly in respect of the alleged obviousness of the subject matter of certain of the claims in the patent.

[29] Dr. Kevin Parkinson is a practising ophthalmologist in British-Columbia. He also possesses hospital privileges at the Coquitlam Cataract Centre and at Ridge Meadows Hospital. He has completed fellowship training in the area of glaucoma, has seen approximately 50,000 patients with this disease and gives lectures on the topic of ophthalmology and glaucoma. He swore two affidavits, dated November 13, 2010 and March 15, 2011, with respect to the subject matter of the '626 Patent, the POSITA to which that patent relates, Sandoz's allegations of non-infringement, and the evidence provided by Sandoz's experts.

B. *Sandoz's experts*

[30] Dr. Henry Jampel is a professor of Ophthalmology at the John Hopkins University School of Medicine. He is also a practicing physician who has treated thousands of patients with glaucoma and related eye diseases. He has been active in research on glaucoma, has held editorial roles with various ophthalmological journals, and is the author of numerous papers and book chapters on

glaucoma and IOP. He provided affidavit evidence with respect to the subject matter of both the '764 Patent and the '626 Patent, the POSITAs to which those patents relate, the allegations in Sandoz's NOA and the evidence provided by each of Allergan's experts.

[31] Dr. Ashim Mitra is the Chairman of the Division of Pharmaceutical Sciences at the University of Missouri. He has conducted extensive research with respect to various drug delivery technologies, including ocular drug delivery. He is the Director for Translational Research at the university's School of Medicine. In that capacity, he is involved in selecting new technologies from bench research, particularly in the ophthalmic area, and co-ordinating pre-clinical studies. His research has focused on the synthesis and formulation of chemical compounds, including in ophthalmic drugs and examining their ability to be transported through membranes into the body. He has published extensively in the field of ophthalmic drugs and has made hundreds of presentations on the topic for various audiences. He provided affidavit evidence with respect to the subject matter of the '764 Patent, the persons to whom that patent is directed, certain of the allegations in Sandoz's NOA and the evidence provided by Mr. Beck.

[32] Allergan raised some serious concerns with respect to the credibility of Dr. Mitra. In short, Allergan referred to a number of U.S. cases in which Dr. Mitra's testimony has been found to be not credible (including *Allergan, Inc v Barr Laboratories, Inc*, 2011 US Dist LEXIS 101778, 09333 SLR, at paras 46-52 (D Del) [*Barr Laboratories*]; *Syntex LLC v Apotex, Inc*, 2006 WL 1530101, C01-02214 MJJ, at para 78 (ND Cal)), or misleading (*Roche Palo Alto et al v Apotex Inc et al*, 526 F Supp 2d 985, at 994 (ND Cal)). Included among those cases was a case in which Dr. Mitra took a position before this Court that was inconsistent, to say the least, with the position he subsequently took before a court in the U.S. (compare *Barr Laboratories*, above, with *Pfizer Canada Inc v*

Canada (Minister of Health), 2009 FC 1294, at para 154). Allergan also drew the Court's attention to inconsistent statements made by Dr. Mitra during cross-examination in the case at bar concerning the fact that, in six of the seven proceedings in which he has recently testified, it was his opinion that the patent was invalid (Applicant's Record, at 940-943). Given the foregoing, I have serious reservations regarding Dr. Mitra's credibility. I have therefore approached his evidence with a considerable degree of caution (*Sanofi-Aventis Canada Inc v Ratiopharm Inc*, 2010 FC 230, at para 17 [*Sanofi*]) and have generally found the evidence of Allergan's witnesses to be more credible and reliable in instances where their evidence has conflicted with his evidence.

III. Issues

[33] Although many issues were raised in Sandoz's NOA and in Allergan's Application, the issues that continue to be pursued by the parties are as follows:

1. Is the allegation that the '764 Patent is invalid on the ground of obviousness justified?

2. Will the product monograph (PM) for the Generic Drug induce infringement of any of the claims in the '626 Patent?

3. Are Sandoz's allegations of non-infringement of the claims in the '626 Patent justified?

4. Is Sandoz's allegation that the '626 Patent is invalid for inutility justified on the basis that either:

   (a) the claims therein cover non-useful subject matter; or

   (b) the utility of that subject matter could not be soundly predicted as of the priority date and the Canadian filing date of the '626 Patent?

IV. Analysis

A. *Is the allegation that the '764 Patent is invalid on the ground of obviousness justified?*

[34] To assess this issue, it is necessary to first construe the claims of the patent and to discern the inventive concept in that patent (*Free World Trust v Électro Santé Inc*, 2000 SCC 66, [2000] 2 SCR 1024, at para 19 [*Free World Trust*]).

[35] Allergan has asserted claims 1-6 and 14-25 of the '764 Patent. The representative claim is claim 22, which narrows the fixed combination drug claimed in claim 1 to the specific fixed combination found in COMBIGAN. Claim 22 refers to claim 6, which in turn refers to claim 3, which in turn refers to claim 1, as follows:

> Claim 22 - Topical use of a therapeutically effective amount of a composition according to claim 6 in an affected eye for treating glaucoma.
>
> Claim 6 - A composition according to claim 3 further comprising from 0.001% by weight to less than 0.01% by weight of benzalkonium chloride.
>
> Claim 3 - A composition according to claim 1, wherein the amount of brimonidine is 0.2 percent by weight and the amount of timolol is 0.5 percent by weight.
>
> Claim 1 - An ophthalmic topical pharmaceutical composition for the treatment of glaucoma or ocular hypertension comprising an effective amount of brimonidine and an effective amount of timolol in a pharmaceutically acceptable carrier therefor.

[36] There is no dispute between the parties regarding the construction of the language in claims 1, 3, 6 and 22 of the '764 Patent (the "Representative '764 Claims"). The parties are in general agreement that those claims describe a fixed combination of brimonidine (0.2%) and timolol (0.5%)

in a pharmaceutically acceptable carrier containing BAK (0.001% to 0.01%) (the "Composition") and the use of the Composition for the topical treatment of glaucoma and ocular hypertension.

[37] The test for assessing obviousness comprises the following four steps:

1. Identify the person skilled in the art and the relevant common general 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; and

4. Without any knowledge of the alleged invention as claimed, assess whether those differences (i) constitute steps that would have been obvious to the skilled person, or (ii) required a degree of invention (*Apotex Inc v Sanofi-Synthelabo Canada Inc*, 2008 SCC 61, [2008] 3 SCR 265, at para 67 [*Sanofi*]).

(1) Step One - The skilled person and the relevant common general knowledge

[38] Dr. Fechtner opined that the POSITA to whom the '764 Patent is addressed "is a person engaged in developing pharmaceutical formulations and treatment for methods for the eye, or is a specialist in treating diseases of the eye such as an optometrist or an ophthalmologist who also has experience in either developing ophthalmic pharmaceutical formulations or in designing and running clinical trials on such formulations" (emphasis added).

[39] Drs. Mitra and Jampel took a similar position, when they stated that the '764 Patent is addressed to pharmaceutical formulators and to ophthalmologists. However, Sandoz subsequently

took the position that the POSITA is a composite of a practicing ophthalmologist and a pharmaceutical formulator. During the oral hearing of this application, Sandoz characterized this difference between the views expressed by Dr. Fechtner and its own experts as being a "minor" and as having no "real effect."

[40] That said, in my view, the POSITA to whom the '764 Patent is addressed is someone who is either a pharmaceutical formulator or a specialist in treating diseases of the eye, as described by Dr. Fechtner. This would include persons such as Drs. Jampel (who conceded in cross-examination that he has no experience with formulations), Fechtner, and Mitra, as well as Mr. Beck. This is consistent with the position taken by Sandoz in its NOA.

[41] Dr. Jampel stated in his affidavit that the common general knowledge of the POSITA as at the Priority Date included the following:

i. a detailed knowledge of ocular hypertension and glaucoma;

ii. a detailed knowledge of the IOP lowering medications in use at that time, including those described at paragraphs 14 to 18, above;

iii. the knowledge that IOP lowering medications were commonly used in combination, either in concomitant use or combined together, in order to obtain adequate IOP lowering, and that the use of two IOP lowering medications resulted in greater IOP reduction in either individual medication alone;

iv. the knowledge that both brimonidine and timolol were well-established IOP lowering medications;

v. the knowledge that brimonidine and timolol had been used in concomitant therapy and that such therapy resulted in a larger IOP reduction than with brimonidine or timolol alone;

vi. the knowledge that commercially available combination products typically included timolol as one of the active ingredients - such products included COSOPT (combination of dorzolamide and timolol that had been available in the U.S. since 1998 and in Canada since 1999), as well as combinations of pilocarpine and timolol and of latanoprost and timolol (Xalacom) that were commercially available outside the United States prior to 2002; and

vii. the knowledge that BAK was a commonly used preservative in ophthalmic solutions.

[42] At the oral hearing of this application, Allergan stated that while there might be some "subtle differences" between its experts and Dr. Jampel, its arguments would be based upon Dr. Jampel's above-described position regarding the common general knowledge of the POSITA as at the Priority Date. Accordingly, I am prepared to accept the foregoing summary provided by Dr. Jampel for the purposes of the present analysis, subject to the following observations.

[43] First, I am satisfied that the evidentiary record demonstrates that a POSITA at the time of the Priority Date would also have been familiar with the fact that Allergan's second generation brimonidine product, ALPHAGAN P, contained (i) 0.15% brimonidine, rather than the 0.2% concentration that is used in the Composition, and (ii) Purite, rather than BAK as a preservative. That person also would have been aware that, when administering brimonidine and timolol

concomitantly, the state-of-the-art was to administer those drugs separately, 5 minutes apart, to avoid the "wash-out" effect.

[44] Second, the record also demonstrates that the POSITA would have been aware of U.S. Patent No. 5,502,052, issued March 26, 1996 (the "DeSantis Patent"), which suggested that anti-glaucoma compositions that comprise a combination of one or more beta-blockers (such as timolol) with one or more alpha-2 agonists (brimonidine was not specifically mentioned) achieve a greater reduction in IOP than that which is achievable with the same concentration of either type of active ingredient used alone.

[45] Third, I am satisfied that the POSITA also would have been aware that the benefits associated with a fixed composition of two active ingredients for use in the topical treatment of glaucoma, relative to concomitant therapy involving those same active ingredients, likely would include: (i) less preservative being administered to patents, and (ii) greater patient compliance with the combined administration.

(2) Step Two - The inventive concept

[46] Sandoz submits that "it is the claims that define the invention" in any patent and that the inventive concept of the '764 Patent must be discerned solely from the language in the claims of the patent.

[47] It is settled law that the "fences" and "boundaries" of the "field" of monopoly conferred by a patent are established by the claims of the patent (*Free World Trust*, above, at paras 14, 33, 51, 66). That said, to achieve a "purposive construction," is permissible to have regard to other parts of the patent "through the eyes of a skilled addressee," to resolve ambiguity and to achieve flexibility and

fairness in differentiating between the essential and the unessential features of the invention (*Whirlpool Corp v Camco Inc*, 2000 SCC 67, [2000] 2 SCR 1067, at para 48 [*Whirlpool*]). Given that there is no dispute in the case at bar with respect to the construction of the claims, there is no need to look beyond the claims of the '764 Patent to ascertain the field of monopoly claimed therein.

[48] The same cannot be said with respect to the inventive concept of the claims.

[49] Generally speaking, the Representative '764 Claims simply claim the Composition for topical use in an affected eye for treating glaucoma. Sandoz submits that the inventive concept of those claims must be discerned from this description alone. Dr. Jampel took the same position.

[50] I disagree. If that were the case, it would not be possible in this and similar cases to fully ascertain the differences between the state-of-the-art and the inventive concept of the claim, for the purposes of performing the third step of the obviousness test.

[51] In cases such as this, where "the inventive concept of the claims is not readily discernible from the claims themselves," it is both necessary and permissible to look to the balance of the patent "to determine its inventiveness" (*Sanofi*, above, at para 77). In other words, "to ascertain the nature of the invention" that is articulated in the claims, and to understand the extent to which the claimed invention differs from the prior art, the Court may "look to the whole of the disclosure" in the patent (*Whirlpool*, above, at para 49(g), quoting *Consolboard Inc v MacMillan Bloedel (Saskatchewan) Ltd*, [1981] 1 SCR 504, at 520-21). That said, it bears underscoring that "it is not permissible to read the specification in order to construe the claims more narrowly or widely than the text will allow" (*Sanofi*, above, at para 77).

[52] In *Sanofi*, above, at paras 77-78, the Supreme Court looked beyond the claims in question, which were confined to "[a] bare chemical formula," in ascertaining the inventive concept of those claims. A similar approach was adopted in *Laboratoires Servier v Apotex Inc*, 2009 FCA 222, at paras 58-59. This was necessarily done after claims construction had been completed, because the exercise of claim construction is antecedent to the assessment of issues concerning validity and infringement (*Free World Trust*, above, at para 19; *Whirlpool*, above, at para 43).

[53] Contrary to Sandoz's submissions, I do not read *Sanofi* as suggesting that, in determining the inventive concept of the claims in a patent, it is only permissible to look beyond the claims of the patent when the claims are confined to a bare chemical formula or to a selection patent. Indeed, the Court in that case specifically noted that its discussion of anticipation and obviousness was "applicable to patents generally" (*Sanofi*, above, at para 29).

[54] The view expressed above is consistent with the approach taken in *Eli Lilly Canada Inc v Novopharm Ltd*, 2010 FCA 197 [*Eli Lilly*], at paras 33, 57, where the Federal Court of Appeal discerned the inventive concept of the claims from the disclosure section of the patent, after observing: "A selection patent is the same as any other patent. Its validity is vulnerable to attack on any of the grounds set out in the Act."

[55] The view expressed above is also consistent with the approach taken by my colleague Justice Mactavish in *Novo Nordisk*, above, at para 113. As in the case at bar, that case concerned a drug patent containing use claims. After concluding that the alleged advantageous properties of the drug repaglinide were not part of the claims because they were not referred to anywhere in the claims, Justice Mactavish observed: "That said, any advantageous properties possessed by

repaglinide would indeed be inherent to the compounds described in those claims, and thus should be taken into account when examining issues such as anticipation and obviousness." Justice Mactavish proceeded to have regard to the alleged properties set out elsewhere in the patent in concluding that the inventive concept of the relevant claims of the patent, which were not confined to a bare chemical formula, included "repaglinide and its surprising pharmacokinetic properties when used to treat diabetes mellitus" (*Novo Nordisk*, above, at paras 186, 308).

[56] In the case at bar, Sandoz and Dr. Jampel submitted that the inventive concept of the claims of the '764 Patent is limited to the Composition itself, for use in treating glaucoma or ocular hypertension. This is essentially what Justice O'Reilly concluded with respect to the only other fixed combination product (COSOPT) that has been approved for topical treatment of glaucoma in North America (*Merck & Co v Canada (Minister of Health)*, 2010 FC 1042, at para 38 [*Merck (2010 FC 1042)*]). As discussed, above, the position of Sandoz and Dr. Jampel on this point was rooted in their view, which I do not share, that the inventive concept of the claims of the '764 Patent must be discerned from the claims themselves.

[57] Allergan submitted that the chemical stability of the Composition was a distinct aspect of the innovative concept of the '764 Patent. In the Background section at the beginning of the patent, reference was made to the recognized need for a composition comprising brimonidine and timolol which, among other things, has "increased stability." However, as Dr. Jampel noted and as Dr. Fechtner conceded, no evidence of such increased stability was disclosed in the patent, or by Allergan's experts. As to whether chemical stability itself is part of the innovative concept of the patent, Mr. Beck conceded that a pharmaceutical product has to have sufficient stability to support its shelf life. Therefore, I prefer to characterize this aspect of the innovative concept as being the

combination of brimonidine (0.2%), timolol (0.5%) and BAK (0.005%) in single stable solution with a pharmaceutically acceptable carrier.

[58] I am satisfied that the inventive concept of the claims of the '764 Patent also includes (i) the improved safety profile of the Composition, (ii) BID dosing without an afternoon reduction in efficiency, and (iii) the reduction in the daily load of preservative administered to patients taking both brimonidine and timolol. Although Allergan submitted that the inventive concept of the claims further includes "[i]ncreased IOP lowering of the combination as compared to monotherapy with individual agents," this was simply baldly asserted and was not further developed in Allergan's written or oral submissions. Accordingly, it will not be further addressed in these reasons.

[59] With respect to the improved safety profile, the Background section at the outset of the '764 Patent noted that "there is a need to increase the efficacy of many topical ophthalmic agents, without increasing the systemic concentration of such topical agents, since it is well-known that many of such topically applied ophthalmic agents cause systemic side effects, e.g., drowsiness, heart effects, etc." The patent then states: "Unexpectedly, it has been discovered that brimonidine in combination with timolol meets these criteria."

[60] After reporting the results of a substantial study comparing the side effect profiles of brimonidine monotherapy, timolol monotherapy and the fixed combination drug claimed by the patent, the disclosure section of the patent concludes by stating:

> The Combination administered BID demonstrated a favorable safety profile that was comparable to Timolol BID and better than Brimonidine TID with regard to the incidence of adverse events and discontinuations due to adverse events.

[61] I accept Dr. Fechtner's opinion that "[t]he POSITA would have considered the improved safety profile [of the fixed combination drug], including the reduction of incidences of adverse events and discontinuance due to adverse events, to be part of the invention claimed in the '764 Patent." That is to say, I accept his view that improved safety profile is part of the inventive concept of the '764 Patent.

[62] With respect to BID dosing without an afternoon reduction in efficiency, Dr. Fechtner reported in his affidavit that the U.S. FDA only approved ALPHAGAN to be administered TID due to concerns of an afternoon reduction (or "trough") in the efficiency of brimonidine when administered BID. Among other things, the clinical trial that was described in the '764 Patent assessed the IOP lowering of the Composition at times 0, 2, 7 and 9 hours. Dr. Fechtner explained that the nine hour measurement was significant because it was taken at a time when it would be expected that patients being administered brimonidine TID would display a greater IOP lowering, due to the effect of the second daily dose of brimonidine (taken about an hour prior to the nine hour measurement). Dr. Fechtner proceeded to observe:

> Despite this, the inventors report [in the disclosure of the '764 Patent] that the fixed combination drug did not demonstrate a trough in efficiency in the afternoon when compared with patients receiving ALPHAGAN administered TID. Surprisingly, the inventors report that mean IOP for patients administered the fixed combination drug (BID) was statistically significantly lower at the 9 hour point and for those patients receiving ALPHAGAN (TID) after 6 weeks and after 3 months … The fact that patients that were administered ALPHAGAN TID did not show lower IOP at the 9 hour time point shows that the inventors had developed a formulation which eliminated the afternoon IOP trough despite BID administration.

[63] With respect to the reduction in the daily load of preservative administered to patients taking both brimonidine and timolol, Mr. Beck reported in his affidavit that his team at Allergan expected

that a reduction in the concentration of BAK might result in a reduction in the efficacy of the Composition. Nevertheless, due to the side effects associated with BAK, his team conducted experiments to investigate whether a lower amount of BAK could be used as a preservative in the Composition. Through their work, the team discovered that a combination of brimonidine and timolol "could be effectively preserved from microbial contamination using only 0.005% BAK; less than half the amount of BAK known to be used by Merck in formulating [COSOPT] and a reduction of 70% from the amount to which the eye is exposed when both drugs are used in monotherapy." Once again, this discovery was described in the disclosure section of the '764 Patent.

(3) Step Three - The differences between the state-of-the-art and the inventive concept

[64] The differences between the prior art discussed at paragraphs 41 to 45 above and the innovative concept of the claims in the '764 Patent are the following: (i) the Composition combines brimonidine and timolol into a single, chemically stable, formulation - that combination had never previously been made or reported in the prior art, (ii) the Composition has a superior safety profile, relative to brimonidine TID, (iii) the Composition permits BID dosing without an afternoon reduction in efficiency, relative to brimonidine TID treatment, and (iv) patients who are treated with the Composition receive a significantly reduced daily load of BAK, relative to concomitant treatment of brimonidine and timolol.

[65] With respect to BID dosing without a reduction in afternoon efficiency, the '764 Patent disclosed, among other things, that in the clinical trial mentioned immediately above, the decreases from baseline diurnal IOP at hour 9 of the daily testing "were greater for the Combination group than for the Brimonidine group at all follow-up visits, although the differences were not statistically significant ($p \geq 0.104$)." Mr. Beck's uncontradicted evidence was that "[t]he frequency of

administration for which a formulation is approved significantly affects its use and value because of the discomfort, difficulty, unpleasantness, and risk of infection associated with installation of eyedrops." For these reasons, Mr. Beck stated that a formulation approved for BID dosing "is, all else being equal, much better than a drug that must be administered three times a day." Once again, this evidence was not contradicted. With respect to the Composition in particular, it requires only two administrations per day, versus the five separate administrations that continue to be required in the United States for patients being administered brimonidine (TID) and timolol (BID) concomitantly, and the four separate administrations that are required elsewhere for that concomitant therapy. For this reason, Mr. Beck stated in cross-examination that a "combination product that had a dosing regimen of two times a day would be considered more advantageous, from a compliance standpoint, than monotherapies dosed" four or five times a day. Again, this evidence was not contradicted.

[66] With respect to the superior safety profile of the Composition, the '764 Patent disclosed, among other things, that in the clinical trial discussed in Example II of the specification, adverse events leading to the discontinuation of patients occurred in only 3.6% (7/193) of the patients who were administered the Composition, versus in 14.3% (28/196) of the patients who were administered brimonidine alone. In addition, it was disclosed that serious adverse events were reduced by 50% for the combination product, relative to monotherapy treatment of brimonidine or timolol. Moreover, it was disclosed that the composition had what may be described as a statistically significant ($p \leq 0.034$) improved allergy profile, compared with brimonidine monotherapy.

[67] Sandoz submitted that various articles referred to by Dr. Jampel in his affidavit, and attached thereto, reported that the efficacy of the Composition was not found to be statistically significant from the efficacy of concomitant treatment of brimonidine and timolol. However, those articles were all published a number of years after the Priority Date, and did not address the common general knowledge of the POSITA as at the Priority Date. Moreover, those articles were not attached to Sandoz's NOA. These important facts distinguish this "post-art" evidence from the cases relied upon by Sandoz. Sandoz was not able to identify any case in which such articles were admitted or given any weight in a proceeding involving an application under the Regulations. In my view, those articles are not admissible, as they are not "probative of a question at issue; in this case, the state-of-the-art at the relevant time" (*Eli Lilly Canada Inc v Apotex Inc*, 2007 FC 455, at para 339). In short, they are not relevant to my determination of the differences between the inventive concept of the '764 Patent and the state-of-the-art as understood by the POSITA as at the Priority Date. As an aside, I would add that even if the Composition is simply as effective as concomitant administration of brimonidine and timolol, it would continue to have other demonstrated advantages over that concomitant therapy, including (i) requiring the administration of only two drops a day versus five in the U.S. and four elsewhere, and (ii) eliminating an afternoon trough, relative to BID administration of brimonidine in monotherapy or concomitant therapy.

[68] In addition, Sandoz submitted that since the alleged invention claimed in the '764 Patent existed once the combination itself was made, the benefits discovered in Allergan's subsequent clinical trials cannot be part of the innovative concept of the patent. Sandoz added that recognition of the superior safety profile of the Composition would require this Court to hold that the invention did not exist until the clinical trial was conducted and the results analyzed.

[69] I disagree. The cases relied upon by Sandoz on this point simply stand for the proposition that the utility of the pharmaceutical patent does not need to be demonstrated by prior human clinical trials (*Apotex Inc v Wellcome Foundation Ltd*, 2002 SCC 77, [2002] 4 SCR 153, at para 77; *Pfizer* (*2009 FC 638),* above, at paras 87-88; aff'd 2010 FCA 242). In the case at bar, the safety data in question was disclosed in the '764 Patent and is a legitimate part of the innovative concept of that patent.

(4) Step Four - Were the differences between the inventive concept and the state of the art obvious?

[70] In *Sanofi*, above, at paragraphs 69 and 70, Justice Rothstein identified a number of factors that should be taken into consideration in cases where it is appropriate to assess whether the invention was "obvious to try." In the case at bar, Allergan conceded that it is appropriate to engage in this assessment, because the Composition is a pharmaceutical invention that was achieved by experimentation (*Sanofi*, above, at para 68; *Bridgeview Manufacturing Inc v 931409 Alberta Ltd*, 2010 FCA 188, at para 42). I agree.

[71] Accordingly, it is appropriate to consider the following factors that were identified by Justice Rothstein:

- 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?

(a) *Was it more or less self-evident that the Composition would work? Were there a finite number of identified predictable solutions known to skilled persons?*

[72] Sandoz submitted that to the extent that there was any recognized need for a product with the alleged benefits of the Composition, it was well known that a combination product would offer such benefits. However, the fact that it may have been known that a combination product such as the Composition would provide particular benefits is not a sufficient basis upon which to conclude that it was more or less self-evident that the Composition would work or that there were any predictable solutions for achieving the Composition known to the POSITA. It is one thing to have an idea that a potential product would or might have certain beneficial properties. It is quite another thing to actually create that product. It is on the latter that this assessment must focus (*Pfizer Canada Inc v Apotex Inc*, 2009 FCA 8, at para 29 [*Pfizer (2009 FCA 8)*]).

[73] A similar response is warranted in respect of Sandoz's submission that a fixed combination of an Alpha2 agonist (a class of drugs that includes brimonidine) and a beta blocker, such as timolol, had been described in the DeSantis Patent. I accept Dr. Fechtner's opinion that the POSITA would not have read the DeSantis Patent as disclosing the combination of brimonidine and timolol. Although that patent stated that "the alpha-2 agonists which can be employed in the compositions of the present invention include all pharmaceutically acceptable compounds which have alpha two agonist activity and are effective in controlling intraocular pressure," I accept Dr. Fechner's position that the class of compounds described "is indefinite, undefined and unknowable." As Dr. Fechtner also pointed out, the DeSantis patent provided no experimental data of any kind to guide the

POSITA in understanding what was included in this broad language. I note that Dr. Jampel acknowledged in cross-examination that (i) "[t]here is an almost unlimited number of ways that this patent of combining an Alpha-2 agonists and a beta blocker could be executed", and (ii) the DeSantis Patent gave no data with respect to efficacy, side effects or stability.

[74] Sandoz observed that the '764 Patent recognized that brimonidine and timolol had been combined in concomitant therapy. Sandoz noted that this is a binding admission as to what constitutes the state-of-the-art, and submitted that Allergan cannot argue that there is anything inventive in using brimonidine and timolol together to treat glaucoma and ocular hypertension. Rather, Sandoz submitted that the invention (which it denies was achieved by Allergan) is confined to the making of a fixed combination product with brimonidine and timolol in "the same bottle."

[75] I do not interpret Allergan to be taking the position that there is anything inventive in using both brimonidine and timolol to treat glaucoma or ocular hypertension. Therefore the focus of the assessment below will be upon whether the differences between the inventive concept and the state-of-the-art discussed at Step Three of this analysis immediately above were obvious. Within the specific context of the "obvious to try" analysis, the focus will be upon whether it was more or less self-evident that the Composition would not only work, but also offer those differences, and whether the solutions for achieving the composition were predictable and known to the POSITA.

[76] In that context, a series of articles appended at Tabs H, I, K and AA to Dr. Jampel's affidavit are of no assistance to Sandoz, because, as Dr. Jampel acknowledged in cross-examination, those articles (i) did not test a combination of brimonidine and timolol, (ii) did not explore the potential BAK levels that could be used in a combination product, and (iii) did not address the allergies or the kinds of other local side effects that can lead to a discontinuance of therapy. Indeed, the duration of

the first three of those studies was limited to the administration of a single drop, two days, and three weeks, respectively, which was too short to test for allergies and other adverse effects that often take much longer to manifest themselves. As noted by Mr. Beck in his affidavit, "allergic conditions would typically not appear to be detectable after a short trial of only a few weeks or less." This evidence was not contradicted.

[77] A fifth study, appended at Tab Z of Dr. Jampel's affidavit, was similarly unhelpful. Although it addressed safety, it did so simply by assessing vital signs and spontaneously reported adverse events. Dr. Jampel did not suggest that the study yielded any useful data in that regard, and Dr. Fechtner's position that the article did not disclose useful safety data was not contested.

[78] Sandoz submitted that the clinical trial reported in the '764 Patent compared the Composition with the monotherapies of brimonidine TID and timolol BID, rather than with the concomitant administration of those active ingredients. In this regard, it noted that the uncontradicted evidence was that (i) the concomitant administration of two glaucoma drugs was a common practice at the time of the Priority Date, and (ii) brimonidine and timolol were among the drugs that were being administered concomitantly at that time. Allergan replied that it had no obligation to expand its clinical trials to include a comparison with concomitant administration of those ingredients. Stated alternatively, while Allergan recognized that it bears the burden of demonstrating the alleged inventive concepts of the Composition, relative to the state-of-the-art as at the Priority Date, it submitted that it had no obligation to create data pertaining to concomitant therapy for the purposes of demonstrating those alleged inventive concepts. Allergan also noted that the uncontradicted evidence of Dr. Fechtner was that the state-of-the-art suggested that the side effect profile of the only other fixed combination drug to have been approved by the U.S. FDA prior

to the Priority Date (COSOPT) was worse than (i) the side effect profile for concomitant administration of the two active ingredients (dorzolamide and timolol), with respect to eyelid pain and discomfort (reported in the Strohmaier study), and (ii) the side effect profile of timolol administered as monotherapy (reported in the Clineschmidt study).

[79] On the particular facts of this case, I agree with Allergan's position on this point. Sandoz was not able to identify any jurisprudence to support its position. In my view, in the absence of any prior art which demonstrated a safety profile for concomitant therapy comparable to that which was reported for the Composition in the '764 Patent, it is entirely appropriate to recognize that superior safety profile as being one of the differences that distinguish the Composition from the prior art.

[80] Sandoz raised a similar argument with respect to Allergan's failure to compare the Composition with brimonidine dosed BID. In this regard, Sandoz noted that brimonidine is approved for BID dosing in Canada and elsewhere outside of the United States. In my view, this argument ignores the important fact that part of the innovative concept of the Composition is that it eliminated the afternoon reduction in efficacy of brimonidine administered BID. As discussed at paragraph 62 above, according to Dr. Fechtner, whose testimony on this point was not contested, this was a significant concern of the U.S. FDA. By overcoming this afternoon reduction in efficiency of brimonidine administered BID, the Composition achieved an innovation, even if the principal commercial benefit of that innovation arose in the United States. In short, this discovery, together with the discovery of a way to formulate brimonidine and timolol together in a chemically stable formula, and the discovery of surprising safety effects, (i) "added to the cumulative wisdom on the subject of" these active ingredients, and (ii) provided a method whereby these discoveries can reduce the incidence of blindness in the population through practical application (*Shell Oil Co v*

Canada (Commissioner of Patents), [1982] 2 SCR 536, at 549; *Calgon Carbon Corp v North Bay (City)*, 2005 FCA 410, at paras 11-13).

[81] Sandoz was unable to identify any jurisprudence to support the position, which I do not accept, that an innovation cannot be recognized in assessing obviousness unless it has value in Canada. Sandoz also provided no support for its inference that the innovation was of no benefit in Canada, where doctors who are concerned about the reduction in afternoon effectiveness of brimonidine BID therapy now have the option of prescribing COMBIGAN.

[82] Sandoz suggested that the Composition was obvious from the prior art because (i) the concentrations of timolol (0.5%) and brimonidine (0.2%) were the same concentrations of those ingredients that were included in other drugs being sold at that time, (ii) the concentration of BAK (0.005%) is the same as in Allergan's ALPHAGAN product, which was launched before the Priority Date, and (iii) the excipients in the Composition are the same as those in Merck's TIMOPTIC product, which also was launched before the Priority Date. In this regard, Sandoz noted that Dr. Fechtner acknowledged in cross-examination that the most prescribed concentration of timolol in the United States at the time of the Priority Date was 0.5%. Sandoz added that there is no discussion in the '764 Patent with respect to any problems encountered in formulating a combination of brimonidine and timolol. It proceeded to assert that "[t]he skilled formulator would be able to easily manufacture such a combination." However, Sandoz never offered any explanation whatsoever as to why no one ever did so (*Beloit Canada Ltd v Valmet Oy* (1986), 8 CPR (3d) 289, at 295; *Janssen-Ortho Inc v Novopharm Ltd*, 2007 FCA 217, at para 24 [*Janssen-Ortho*]).

[83] Sandoz observed that Mr. Beck admitted in cross-examination that it was "not problematic" to make the combination product. In my view, this seriously mischaracterizes Mr. Beck's evidence.

In the passages of his cross-examination to which Sandoz referred, Mr. Beck's response was confined to what he characterized as being "the actual physical combining of the various active and inactives." He explicitly distinguished between "the simple compounding of the formula in its inaqueous solution," which he characterized as being "not difficult to do," and the obstacles that he and his team encountered "from a chemical standpoint." Those obstacles are discussed at paragraphs 96 to 103 below.

[84] I accept Dr. Fechtner's statement that the improved safety profile of the Composition is remarkable and could not have been predicted in advance of creating the Composition and conducting experimentation to ascertain the results. I note that, in cross-examination, Dr. Jampel could not identify any prior art which demonstrated that the concomitant administration of brimonidine in timolol BID reduced side effects. In addition, he ultimately conceded that the improved side effects disclosed in the '764 Patent were "unexpected." The unexpected nature of the improved safety profile of the Composition is further corroborated by Mr. Beck's statement that he and his colleagues did not predict the improved allergy profile of the Composition and that they considered the results of the clinical trial with respect to that improved allergy profile to have been surprising.

[85] I also accept Dr. Fechtner's statements that the POSITA would have known that (i) potential problems might be encountered when formulating brimonidine and timolol into a fixed combination drug, and (ii) "differences in pharmacokinetics, the additive nature of adverse effects with multiple drugs, and potential drug interactions were difficulties to be overcome in developing a fixed combination drug." The various unexpected difficulties encountered by Mr. Beck and his team are discussed at paragraphs 96 to 103 below. The significant time and effort that Mr. Beck and his team

spent overcoming those difficulties lend credence to Dr. Fechtner's statement that it would not have been self-evident or obvious to the POSITA that a chemically stable Composition could be achieved. Dr. Fechtner's conclusion on this point is further supported by Mr. Beck's statement, which I find credible, that each time he and his team began with a new potential formulation, they believed that it could fail at any stage of the process.

[86] In addition, the significant adverse side effects that were known to exist with BAK lend credence to Dr. Fechtner's opinion, which I accept, that the POSITA would not have initially selected BAK as the preservative for the Composition.

[87] In response to all of the foregoing, Sandoz submitted that the POSITA would have started the testing process with a formulation based on TIMOPTIC, including timolol with a concentration of 0.5% and BAK as the preservative. In the latter regard, Dr. Mitra stated that BAK is the preservative in the majority of all ophthalmic products including IOP lowering products. He also stated that the POSITA would have had no reason to seek to replace BAK, which is the preservative in TIMOPTIC and in ALPHAGAN, with another preservative. With respect, this fails to address that BAK was known to have adverse cytotoxic effects and was replaced by Purite in Allergan's second generation ALPHAGAN product, ALPHAGAN P. For that reason, Dr. Jampel conceded that if the POSITA used ALPHAGAN P as his starting point, he would have ended up with a formulation that contains Purite, rather than BAK. Dr. Jampel also acknowledged that, by March 2001, the POSITA would have been aware that (i) Purite was a preservative in ALPHAGAN P, (ii) Purite had a "gentler side effect profile than BAK," and (iii) ALPHAGAN P was formulated at 0.15 percent brimonidine, rather than the 0.2% used in ALPHAGAN.

[88] Dr. Mitra also stated that the mechanism of action of Purite would suggest that it would be an inappropriate preservative for a formulation containing timolol. He added that the POSITA would have realized that Purite may oxidize the sulfur of the timolol molecule. I place little weight on this evidence because (i) as discussed at paragraph 32 above, there have been serious credibility issues raised with Mr. Mitra as a witness, (ii) I accept Dr. Fechtner's position that the prior art (namely, ALPHAGAN P) taught away from the use of BAK, based on its known adverse side effect profile and Allergan's successful formulation of ALPHAGAN P with Purite, and (iii) I find it difficult to accept that Allergan would have undertaken the time and expense associated with attempting to formulate a solution with Purite, if it was self-evident that Purite would not work with timolol. The latter observation also applies to the time and effort that Allergan spent attempting to (i) formulate a product with other active ingredients, including the Brimo X and Synergel formulations, and (ii) determine the appropriate concentration of BAK to use in the Composition.

[89] Dr. Mitra suggested that the POSITA would have known that a fixed combination of timolol and brimonidine could be formulated with a concentration of 0.005% BAK, because brimonidine may have some anti-bacterial activity, such that the 0.01% concentration of BAK that is used with timolol alone could be reduced by 50%. However, in cross-examination, it was apparent that he was simply speculating on this point, because he stated that brimonidine, "being an active ingredient, maybe has some antibacterial activity so that you don't need .02 … 01; half is enough" (emphasis added). He subsequently acknowledged that he had not investigated this matter.

[90] Sandoz further submitted that the POSITA would not have considered using Purite because that substance is patented by Allergan. However, this fails to recognize that the POSITA is a hypothetical person who is able to take into consideration all prior art, including that which may

enjoy patent protection (see, for example, *Eli Lilly Canada Inc v Apotex Inc*, 2009 FC 320, at para 50, and Roger T. Hughes, *Hughes and Woodley on Patents*, 2ed., loose-leaf (Markham, Ont.: Lexis Nexis Butterworths, 2005), ch 5 at 166.4).

[91] In summary, given all of the foregoing, I find that (i) it would not have been more or less self-evident to the uninventive POSITA that formulating brimonidine and timolol into a chemically stable fixed combination drug ought to work, and (ii) there was not a finite number of identified predictable solutions known to skilled persons.

(b) *What was the extent, nature and amount of effort required? Were routine trials carried out or is the experimentation prolonged and arduous, such that the trials would not be considered routine?*

[92] As has been noted, Sandoz submitted that the skilled formulator would have been able to easily manufacture the Composition.

[93] In addition, Sandoz submitted that the time and effort spent by Mr. Beck and his team to develop the Composition were "routine." In this regard, Sandoz asserted that (i) the inclusion and exclusion criteria for the clinical trial discussed in the '764 Patent were typical of those used in clinical trials for IOP lowering drugs, (ii) the criteria for evaluation were typical, (iii) the safety criteria would be included in most, if not all, clinical trials of drugs to treat glaucoma and ocular hypertension, (iv) the methodology was typical of a clinical trial of ophthalmic drugs prior to the Priority Date, (v) the study design was typical, and (vi) the type of data collected was typical. Sandoz maintained that "there is no invention in doing what is routine, even if unexpected results occur."

[94] I disagree with Sandoz's positions that (i) a skilled formulator would have been able to easily manufacture the Composition, and (ii) the time and effort spent by Mr. Beck and his team to develop the composition were "routine."

[95] In my view, Mr. Beck described, in a forthright and credible manner, a significant number of difficulties that he and his team encountered in their development of the Composition. Based on his evidence, and the supporting evidence of Dr. Fechtner discussed in the section immediately above, I am satisfied that the skilled formulator would not have been able to easily manufacture the Composition, and that the efforts undertaken by Dr. Beck and his team to develop the Composition were not "routine."

[96] Mr. Beck explained that, at the inception of the development project, his team considered additional or alternative beta blockers to timolol. They also considered different salt forms of the beta blocker as well as a formulation that did not contain an alpha-2 agonist (such as brimonidine). At that point in time, Mr. Beck stated that he did not know whether or not it would be even possible to formulate a combination product with 0.5% timolol. While he acknowledged that a 0.5% solution of timolol had been sold for many years, he explained that he could not have known in advance whether he could achieve a safe, stable and effective formulation with that concentration in combination with another active ingredient. I accept his statement that "regardless of the fact that timolol was marketed [before the Priority Date] at 0.5 percent, it had no bearing on what I could do as a formulator formulating a new product."

[97] After initially considering multiple formulation candidates, Mr. Beck and his team began with a "Brimo X" (ALPHAGAN P) formulation that contained Purite and perhaps carboxymethyl cellulose (CMC). When they were unable to move forward with that formulation, they switched to a

formulation they called Synergel. Among other things, one of the benefits that they hoped to achieve with Synergel was the sustained release of the drug, which was considered to be an optimal objective. It was only after they abandoned Synergel that they attempted to work with a formulation that included timolol.

[98] In working with timolol, Mr. Beck and his team began by using Purite as a preservative rather than BAK, because BAK was known to be cytotoxic, i.e., it comprises cell membranes. Due to those cytotoxic side effects, Allergan developed and launched ALPHAGAN P with Purite, which was approved by the U.S. FDA in 2001. That said, Mr. Beck and his team recognized that it is much more difficult to maintain the stability of Purite in formulations. During initial stability studies with timolol, they also considered alternate salt forms, including the free base and a heptahydrate salt form.

[99] Approximately two months after beginning their work with a formulation containing Purite and timolol, it became apparent that the timolol in the formula was degrading faster than the team expected (due to its interaction with Purite) and would not meet the minimum 24 month preservative efficacy requirement. Therefore, the team began to work with a formulation containing BAK, with a phosphate buffer system that was similar to that in Merck's TIMOPTIC product.

[100] In attempting to formulate a product with BAK, the team conducted titration studies with concentrations of BAK ranging from 0.01% to 0.002%. Notwithstanding the fact that BAK was used in a 0.005% concentration in ALPHAGAN, the team did not know what minimum concentration would be safe and effective for the Composition. After discovering that the formulation passed the preservative efficacy test with a BAK concentration of 0.002%, the team balanced their objective of having a margin of safety with their objective of minimizing the

concentration of BAK in the formulation, by settling on a concentration of 0.005% for the Composition.

[101] However, two months into their stability studies with that formulation, they once again discovered degradations. Mr. Beck stated that those degradations were novel and entirely unexpected and that the team did not know whether they would be toxic or unsafe for use in humans. Ultimately, they turned out to be harmless. However, this was another unexpected "obstacle" that was encountered in the testing process, and that led Allergan to incur additional time and expense in formulating the Composition.

[102] In addition to the foregoing, Mr. Beck explained that brimonidine and timolol have optimal pHs that are significantly different. He stated that the pH of ALPHAGAN (brimonidine) is most stable at a pH of about 6.3, whereas the pH of timolol is most stable at a pH of approximately 6.9. His uncontradicted evidence, which I accept, was that he and his team could not predict whether or not those two active ingredients would be stable at any pH level.

[103] In summary, before arriving at the final Composition, Mr. Beck and his team:

i. considered other active ingredients;

ii. encountered failures with their Brimo X and Synergel formulations;

iii. encountered a failure with the preservative that they considered to be superior to BAK and had used in their ALPHAGAN P product (that was approved by the U.S. FDA shortly before the Priority Date); and

iv. encountered novel degradations when brimonidine and timolol were combined with BAK.

[104] Based on the foregoing, I find that Mr. Beck and his team (i) engaged in a significant amount of difficult, non-routine work and overcame several unexpected obstacles to develop the Composition, and (ii) did not spend any significant amount of time and effort pursuing possible formulations that would not have been pursued by the POSITA.

[105] In support of its position that the time and effort spent by Mr. Beck and his team to develop the Composition were "routine," Sandoz relied upon *Novo Nordisk*, above, at paragraphs 308 to 319. However, in my view, that case is distinguishable. The inventive concept there was the drug repaglinide and its "surprising pharmacokinetic properties" when used to treat diabetes mellitus. Among other things, there was evidence in that case that "it was more or less self-evident that repaglinide's pharmacokinetic properties could well be very different from those of [the other enantiomer in the racemate compound]." Moreover, Justice Mactavish determined that "the extent, nature and amount of effort required to make repaglinide in the first place was neither prolonged nor arduous, and the methods used in processes followed to test its pharmacokinetic properties were admittedly routine." In addition, "both sides agreed that the anti-diabetic field was intensely competitive at the time, and that there was a strong demand for a better anti-diabetic medication that did not have some of the drawbacks of the conventional SFU treatments." Moreover, it was found that "[a]dditional motivation to separate and test enantiomers was provided by the impending move towards increasingly stringent regulatory requirements." Justice Mactavish noted that during the relevant period, "there was a strong motivation to find a better antidiabetic medication, given the intense competition field." She then found that (i) "it was self-evident that a person skilled in the art

would test enantiomers for their pharmacokinetic properties," and (ii) there was evidence that "the testing of enantiomers for their pharmacokinetic properties have become a routine part of industry practice as of the relevant date and was not an inventive step by the [Applicant's] drug development team." (*Novo Nordisk*, above, at paras 308-322).

[106] By contrast, in the case at bar, I have found that it would not have been self-evident to the POSITA that formulating brimonidine and timolol into a chemically stable fixed combination drug ought to work. While the prior art may well have suggested to the POSITA that such a drug would be "worthwhile" to pursue, that would not be a sufficient basis upon which to conclude that the Composition was obvious (*Pfizer (2009 FCA 8)*, above, at para 45). In addition, there was no evidence that a POSITA would have had any basis whatsoever for believing that the Composition ought to (i) have a superior safety profile, relative to brimonidine TID, or (ii) permit BID dosing without an afternoon reduction in efficiency, relative to brimonidine TID treatment. These discoveries were made only after the completion of a large clinical trial involving 586 individuals, which began as a three-month study and was then expanded to include a nine-month masked extension. Dr. Fechtner characterized the data collected during that trial as being "at the high end for a clinical trial." Moreover, there was no evidence in the case at bar to suggest the existence of any competition, let alone intense competition, to develop a fixed combination drug comprising brimonidine and timolol. There was also no evidence that the type of testing conducted by Mr. Beck and his team to develop the Composition had become a routine part of industry practice prior to the Priority Date. Furthermore, as discussed below, I have determined that there was not a strong motive provided in the prior art to develop a solution such as the Composition. Finally, I am satisfied that the nature and amount of effort required by Mr. Beck and his team to develop the Composition, as described above, was prolonged and arduous. I note that a similar conclusion was

reached in the U.S. proceedings between the parties involving COMBIGAN (*Allergan, Inc v Sandoz*, 2:09-cv-00097 TJW, at para 122 (ED Tex 2011)), although I recognize that there are significant differences in (i) the applicable law in this area in Canada and the U.S., and (ii) the evidentiary records in that case and the case at bar.

[107] In support of its position that the trials conducted by Mr. Beck and his team were routine, Sandoz noted that Mr. Beck acknowledged in cross-examination that the cost of developing a new chemical entity can be in excess of $100 million. Sandoz submitted that the $26.4 million which Mr. Beck stated was spent by Allergan developing the Composition was small by comparison, and suggests that the nature and amount of effort required to develop the composition was not prolonged and arduous.

[108] I disagree. In the context of an assessment of obviousness and the particular factual matrix of this case, the fact that it may cost in excess of $100 million to develop an entirely new chemical entity provides little helpful information in determining whether the $26.4 million that was spent by Allergan to develop the Composition is indicative of routine, as opposed to prolonged and arduous, work. Sandoz was unable to identify any jurisprudence to support the proposition that an amount in the range of $26.4 million is, in itself, indicative of work that is merely routine.

[109] A fundamental shortcoming with this particular $100 million benchmark is that it does not provide a useful measure of what might be considered sufficiently routine to weigh in favour of a conclusion that the invention of the Composition was obvious to try. It simply provides a measure of what may be routinely required to invent an entirely new chemical entity. Moreover, in the absence of additional information, the utility of any particular monetary benchmark may often be limited. For example, a level of expenditure that may be indicative of work that is routine in the

presence of a high motivation may well be indicative of work that is not routine where such motivation is not present.

[110] In response to my request for jurisprudence that is more helpful in distinguishing between effort that is routine and effort that is prolonged and arduous, as contemplated by *Sanofi*, above, at paragraph 69, Sandoz referred to *Schering-Plough Canada Inc v Pharmascience Inc*, 2009 FC 1128 [*Schering-Plough*]. There, my colleague Justice Snider concluded that the steps that had been taken by the applicant to develop a new drug were not "overly arduous or complex," but rather appeared to have been somewhat "routine pre-formulation experiments." She therefore concluded that "this factor would tend to operate in favour of a finding of obviousness, although not strongly so" (emphasis added) (*Schering-Plough*, above, at para 209).

[111] In that case, the inventive concept of the patent in question consisted of avoiding lactose and other acidic excipients as the carrier medium and using a basic salt to stabilize the composition (*Schering-Plough*, above, at para 200). In reaching her conclusion regarding the routine nature of the experimentation that had been undertaken by the applicants, Justice Snider concluded that the step of identifying the incompatibility between the active ingredient (descarboethoxyloratadine (DCL)) and lactose "was more or less self-evident" (para 204). With respect to the use of a basic salt, she was skeptical of the respondents' position that this was "more or less self-evident" (para 206), but then proceeded to reach her conclusion regarding the routine nature of the experimentation in question, after considering certain evidence (para 208). Among other things, that evidence did not include anything analogous to (i) the failures that Mr. Beck and his team encountered with their Brimo X and Synergel formulations, or (ii) the failure that they encountered with Purite. Accordingly, *Schering-Plough* is distinguishable. There was also no evidence to suggest that a trial

consisting of over 500 persons was undertaken, let alone the additional two trials that Mr. Beck stated were undertaken.

[112] In the course of its arguments regarding the alleged "routine" nature of the work undertaken by Mr. Beck and his team, Sandoz suggested that I draw an adverse inference from the fact that Allergan failed to provide more evidence regarding the steps that were taken to develop the Composition. In this regard, Sandoz suggested that Allergan should have provided laboratory notebooks, reports and presentations that were made with respect to the Purite degradation issue, documents dealing with the accelerated stability tests that were undertaken and other documentation relating to the testing that was performed. Sandoz asserted that these documents were being "hidden" from this Court.

[113] I have some sympathy for Sandoz's position on this point. Nevertheless, if Sandoz truly thought that anything in that documentation may have supported its allegation of obviousness, it should have availed itself of its opportunity to serve a direction, under Rule 91 of the *Federal Courts Rules*, SOR/98-106, on Mr. Beck to attend and produce that documentation for inspection. It could also have attempted to simply request Allergan's counsel to provide that documentation. Given that it did neither of these things, I declined to draw the requested adverse inference.

(c) *Was there a motive provided in the prior art to combine brimonidine and timolol into a fixed combination?*

[114] Sandoz submits that the prior art disclosed a motive to develop the Composition because it was known that patient compliance likely would be better with fewer daily administrations of drops to the eye, and that the daily preservative load delivered to a patient would be less with a fixed combination drug. This position was undermined by the statement in Dr. Jampel's affidavit that he

did not recall having ever heard of the "long felt need for an effective and safe ophthalmic pharmaceutical composition including brimonidine and timolol," described in the '764 Patent. In cross-examination, Sandoz's position on this point was virtually negated when Dr. Jampel affirmed that he was not aware of any particular motivation among person skilled in the art to combine brimonidine and timolol, although, he speculated that pharmaceutical companies might have such a motivation.

[115] Dr. Fechtner's uncontradicted evidence on this point, which I accept, is that:

(i) the known difficulty in obtaining U.S. FDA approval for fixed combination drugs for the treatment of glaucoma was a major disincentive against the development of such drugs, and the POSITA would not have been motivated to develop a fixed combination drug containing timolol and brimonidine;

(ii) the extent of time, effort and resources required to conduct the clinical trials described in Mr. Beck's affidavit would have given rise to a disincentive for the POSITA to pursue the development of the Composition; and

(iii) the cost of the work required to develop such a drug would have been a further disincentive for the POSITA.

[116] Another statement made by Dr. Fechtner that is relevant to this consideration is that the POSITA would have been well aware that combining two drugs into a fixed combination may lead to the over-administration or under-administration of one of the active ingredients, which is apparently what happened with the combination product of pilocarpine and epinephrine.

(d) *Summary of "obvious to try" assessment*

[117] It follows from the conclusions reached under the headings (a) to (c) immediately above that combining brimonidine and timolol into a fixed combination drug is not something that would have been "obvious to try" for the POSITA. In short, (i) it was not more or less self-evident that the steps that were undertaken to achieve a chemically stable formulation of the Composition ought to work, (ii) the experimentation undertaken to achieve that formulation was not routine, (iii) Allergan did not have a strong motivation to pursue that experimentation, and (iv) the course of conduct undertaken to achieve the Composition does not suggest that the Composition was obvious.

[118] Sandoz submitted that the facts of the case at bar are similar to those that were addressed in *Merck (2010 FC 1042)*, above, where Justice O'Reilly concluded that the only other fixed combination anti-glaucoma drug that has been approved for use in Canada (COSOPT) would have been obvious for the POSITA to formulate.

[119] I disagree. In my view there are significant differences between the content of the patents and the evidence adduced in the two cases. The key passages from *Merck (2010 FC 1042)*, are as follows:

> [47] There is nothing in the patent itself that suggests that there was anything inventive about the co-formulation of a [carbonic anhydrase inhibitor (CAI)] and a beta blocker. No difficulties are mentioned. The patent sets out 32 different examples of co-formulation. Nothing suggests that co-formulation was as difficult as Merck's experts thought it might have been. I have no evidence before me as to the steps the inventors took to arrive at the co-formulation. In the circumstances, all indications seem to be that co-formulation was routine. I have no evidence from Merck about any difficulties or arduous experimentation being required to arrive at a co-formulation. Nor do I have any evidence of difficulty in arriving at an acceptable pH …
>
> …

> [49] While Merck's experts might have been surprised that dorzolamide could be effective when dosed twice daily with timolol instead of three times daily, this effect was clearly disclosed in both Gunning and Nardin. A skilled person would have expected the same effect in a co-formulation of the two agents.
>
> …
>
> [52] No evidence of difficult or prolonged experimentation to achieve a co-formulation was tendered. Indeed, no evidence about the course of conduct leading to a co-formulation was provided. The prior art and the general common knowledge in the field would have motivated a skilled person to attempt to co-formulate dorzolamide and timolol. It was obvious.

[120] By contrast, the '764 Patent included a significant amount of data to support the surprising findings of safety and of the absence in a reduction of afternoon efficiency for the Composition, relative to TID dosing of brimonidine. As has been discussed, these effects were not disclosed in the prior art. Moreover, Mr. Beck's uncontested evidence demonstrates that he and his team encountered a number of unexpected difficulties in developing the Composition, and pursued a number of unsuccessful formulations before finally arriving at the Composition. In short, *Merck (2010 FC 1042)* is distinguishable from the case at bar in several important ways.

(e) *The Actual course of conduct of the inventors*

[121] In *Sanofi*, above, at paragraph 70, it was noted that another factor that may be important in assessing obviousness is the actual course of conduct which culminated in making the invention. In this regard, the Court observed that "if the inventor and his or her team reached the invention quickly, easily, directly and relatively inexpensively, in light of the prior art and common general knowledge, that maybe evidence supporting a finding of obviousness, unless the level at which they worked and their knowledge base was above what should be attributed to the skilled person" (para 71).

[122] Based on the information discussed paragraphs 96 to 103 above, I find that this factor weighs in favour of a finding that the Composition was not obvious. In short, Mr. Beck and his team did not develop the Composition "quickly, easily, directly and relatively inexpensively, in light of the prior art and common general knowledge." On the contrary, they pursued at least three "wild goose chases" (*Sanofi*, above, at para 71) and encountered a number of other obstacles before they finally developed the Composition.

(f) *Commercial success*

[123] A secondary factor that can be relevant in the assessment of obviousness is whether an invention has achieved commercial success. This factor may be indicative of a motivation to fill the commercial market, which may in turn suggest inventive ingenuity (*Janssen-Ortho*, above, at para 25). Indeed, to the extent that commercial success may reflect a view of the marketplace, or a segment thereof, that the invention is superior to previously available products, such success is suggestive of inventive ingenuity, even in the absence of a motivation to fill the commercial market. That said, commercial success may also simply reflect considerations unrelated to the invention, such as marketing skills and market power. Accordingly, in the absence of evidence indicating that commercial success is suggestive of inventive ingenuity, rather than the other factors just mentioned, commercial success may merit little weight in the overall assessment of obviousness.

[124] In the case at bar, Mr. Beck stated in his affidavit that Allergan achieved total sales of COMBIGAN in Canada of approximately $35 million between January 2005 and November 2010. Among other things, estimated that in 2009 and 2010, COMBIGAN held approximately 6% of total sales of anti-glaucoma drugs in Canada.

[125] There is evidence to suggest that the commercial success of COMBIGAN is at least in part attributable to the favourable safety dimension of the inventive concept of the '764 Patent. In short, Dr. Fechtner's uncontradicted evidence is that "one of the reasons why COMBIGAN has been a successful product commercially (and one of the reasons I prescribed it) is because it has an advantageous side effect profile when compared to its components and other available treatment options." This evidence was not contested by Sandoz's experts.

[126] It would have been helpful to have additional information regarding total worldwide sales of COMBIGAN and regarding the size of the market in which it competes. Nevertheless, I am satisfied, on the basis of the information discussed above, that the commercial success of COMBIGAN is a factor that weighs slightly in favour of concluding that the Composition was not obvious.

(5) Conclusion on obviousness

[127] Allergan has met its burden of establishing, on a balance of probabilities, that Sandoz's allegation that the '764 Patent is invalid on the ground of obviousness is not justified. For the reasons summarized in paragraph 117 above, this would remain true even if the inventive concept of the claims of the '764 Patent did not include the uncontested surprising improvement in safety, the elimination of the afternoon reduction of effectiveness and the reduction in daily load of BAK, relative to concomitant treatment of brimonidine and timolol. These additional aspects of the inventive concept simply serve to further strengthen that the invention claimed by the '764 Patent was not obvious.

B. *Will the PM for the Generic Drug induce infringement of any of the claims in the '626 Patent?*

[128] The '626 Patent describes a "new method of protecting the optic nerve and retina of the mammalian eye from damage by glaucoma and other noxious provocations." It is common ground between the parties that this describes a neuroprotective use of the compounds claimed in the '626 Patent, including brimonidine.

[129] In its NOA, Sandoz alleged that the claims of the '626 Patent would not be infringed by the Generic Product. In response, Allergan submitted in its Application in this proceeding that Sandoz's sale of the Generic Product will infringe and/or induce infringement of at least claims 1, 2, 20 and 21 of the '626 Patent. With respect to inducement, Allergan asserted that the proposed indications in the PM will induce physicians, pharmacists and/or patients to infringe the claims of the patent.

[130] In his November 2010 affidavit, Dr. Parkinson explained Allergan's position regarding inducement. In brief, he stated that, Sandoz's PM identifies two indications for the Generic Drug, namely, (i) the lowering of IOP to treat open-angle glaucoma, and (ii) the reduction of long-term fluctuation in IOP, in order to slow or prevent nerve cell injury or death. Regarding the latter indication, he stated that the POSITA would have known as of January 1997, the publication date of the '626 Patent, that long-term fluctuation in IOP was a noxious action that would result in damage to optic nerve cells in some patients. He concluded by asserting that Sandoz's PM "will induce ophthalmologists to prescribe and induce patients to use [the Generic Product] for the treatment of long-term fluctuation and IOP (a noxious action) to inhibit or prevent new cell injury or death."

[131] Allergan has now abandoned that position. Instead, it has submitted that one of the sentences in Sandoz's PM and one of the documents identified in the list of references at the back of the PM

are directed to a neuroprotective use of brimonidine that is unrelated to the reduction of IOP, and will therefore induce infringement.

[132] For the reasons set forth below, I disagree.

[133] Sandoz objected to Allergan's new position regarding inducement on the procedural basis that this theory was not articulated in its Notice of Application. However, I am satisfied that Allergan's current position is a response to the position taken by Dr. Jampel in his affidavit, where he argued that the POSITA would have known in 1997 that the '626 Patent describes and claims protecting the optic nerve cells by directly fortifying those cells, not by having an effect on a noxious action. I agree with Allergan that it is now too late for Sandoz to raise this objection, given that (i) Sandoz did not take the position that it would be prejudiced if this Court were to allow Allergan to advance its new theory of inducement at a late stage in these proceedings, and (ii) Sandoz did not seek leave to adduce additional expert evidence in response (*Abbott Laboratories Ltd v Canada (Minister of Health)*, 2007 FCA 251, at para 35).

(i) *The asserted claims -'626 Patent*

[134] Allergan is asserting claims 1, 2 and 14 of the '626 Patent (the "Asserted Claims"). Claim 14 is dependent on claims 1 and 2 and limits the compounds claimed to brimonidine. Taken together, these claims read as follows:

> Claim 14 (read with claim 1) - Use of an effective amount of brimonidine to inhibit or prevent nerve cell injury or death for protecting the retinal or optic nerve cells in a mammal suffering a noxious action or at risk of experiencing a noxious action on said nerve cells.
>
> Claim 14 (read with claim 2) - Use of brimonidine to inhibit or prevent nerve cell injury or death in the manufacture of a medicament for protecting the retinal or optic nerve cells in a

> mammal suffering a noxious action or at risk of experiencing a noxious action on said cells.

(ii) *The POSITA - '626 Patent*

[135] Dr. Parkinson described the POSITA to which the '626 Patent relates as "a resident ophthalmologist with 2-3 years of experience or a general community ophthalmologist with 1 year of experience treating patients." Dr. Jampel disagreed. He opined that the POSITA "is a researcher with interest, skill and experience in experimental research of the eye diseases, particularly glaucoma." He added: "such a person would have a MD degree or a PhD degree and experience in conducting and analyzing both animal studies and human clinical trials."

[136] The basis for Dr. Jampel's opinion on this point included the following:

i. When the '626 Patent was published in 1997, neuroprotection was only the subject of experimental research.

ii. At that time, no medication had been approved as a neuroprotective agent for patients with ocular hypertension or glaucoma.

iii. The '626 Patent does not provide any information with respect to the clinical application of any invention disclosed in the patent - it simply provided a very large (5000 fold) difference that would be of no use to a practicing ophthalmologist.

iv. Certain data provided in the patent are only relevant to experimental studies and are not described in terms used by ophthalmologists.

v. The examples of the patent relate to testing on cells or in animals and do not provide any basis upon which the purported invention of the '626 Patent could be used clinically.

> Indeed, the persons meeting Dr. Parkinson's definition of the POSITA would have, at best, limited understanding of these examples and their results and would not be able to use the results in clinical practice.

[137] Based on the foregoing, Sandoz submitted that Dr. Parkinson is not a POSITA and that therefore his opinions should be given little weight.

[138] In response, Allergan noted that the '626 Patent mentions glaucoma and IOP no less than 35 times, and that Sandoz did not refer to a single case to support the proposition that an expert needs to know how to perform the experiments described in a patent to provide an opinion regarding the subject matter of the patent. Allergan further noted that it is now established that "a patent specification is a unilateral statement by the patentee, in words of his own choosing, addressed to those likely to have a practical interest in the subject matter of his invention (i.e., 'skilled in the art'), by which he informs them what he claims to be the essential features" (emphasis added) (*Whirlpool*, above, at para 44, citing *Catnic Components Ltd v Hill & Smith Ltd*, [1982] RPC 183, at 242-43).

[139] Upon further review of the '626 Patent, I am satisfied that it is directed towards persons fitting the definitions given by both Dr. Parkinson and Dr. Jampel. In my view, the POSITA is a composite of such persons (*Laboratoires Servier v Apotex Inc*, 2008 FC 825, Snider J., at para 103). In short, contrary to Dr. Jampel's position, it is readily apparent to me that the '626 Patent is also directed towards ophthalmologists such as Dr. Parkinson who may have a clinical and practical interest in the invention disclosed by the '626 Patent. For example, I am satisfied that much of the information under the headings "Background of the Invention," "Summary of the Invention," "Drawings," "Human dosage and administration" and "Measurement of the effects of drug tests for neuroprotective properties" would be of potential interest and value to ophthalmologists.

[140] In the event that I am found to have erred on this point, I agree with Allergan's position that Dr. Parkinson's evidence (i) is nevertheless material to various issues that have been raised in respect of the '626 Patent, and (ii) goes beyond the knowledge that this Court is expected to have. Therefore, his evidence should be admitted and given the weight that I consider to be appropriate (*Merck & Co Inc v Pharmascience Inc*, 2010 FC 510, at para 31).

(iii) *Claims construction*

[141] There is no material dispute between the parties with respect to the construction of the Asserted Claims. In short, although the parties had competing constructions at the outset of these proceedings, Allergan is now conceding Sandoz's construction.

[142] It is now agreed that the '626 Patent relates to a purported new use of certain compounds identified in the patent as "Formula I," and that one of the compounds included in Formula I is brimonidine. The new claimed use is "to inhibit or prevent nerve cell injury or death … for protecting the retinal or optic nerve cells in a mammal suffering a noxious action or at risk of experiencing a noxious action on said nerve cells."

[143] The patent states that there "is an unmet need for agents that have neuroprotective effects in the eye that can stop or retard the progressive damage that occurs to the nerves as a result of glaucoma or other ocular afflictions." This need is said to arise because lowering IOP by administration of drugs or by surgery "is not always effective in obviating damage to the nerves in glaucomatous conditions." Moreover, "[s]ome glaucoma patients never have higher than normal IOP and others continue to develop optic nerve damage despite maximal lowering of IOP."

[144] The promise of the '626 Patent is therefore that the compounds specified in the claims, including brimonidine, will have this purported neuroprotective effect upon retinal or optic nerves in

humans. As the parties now agree, this effect is achieved through a mechanism unrelated to IOP, which helps to shield ocular nerve cells from damage from noxious actions. This use is distinct from the previously known and practised use of brimonidine to treat elevated IOP, and is claimed in the patent to be "particularly effective when administered as a prophylactic treatment, i.e., before damage to the nerve takes place, or before long-term progression of the disease, such as glaucoma, has taken place."

(iv) *Inducement of infringement - the legal test*

[145] To establish infringement of a use claim by inducement, it is necessary to demonstrate the following three things:

i. an act of infringement was completed by a direct infringer;

ii. the infringement was influenced by the inducing party to the point that, without that influence, the infringement would not have taken place; and

iii. the inducing party knew that its influence would result in the completion of the act of infringement.

(See: *AB Hassle v Canada (Minister of National Health and Welfare)*, [2002] 3 FC 221; *Solvay Pharma Inc v Apotex Inc*, 2008 FC 308, at paras 136-137; *Sanofi-Aventis Canada Inc v Novopharm Ltd*, 2007 FCA 167, at paras 9-11 [*Sanofi (2007)*]).

[146] Inducement is a question of fact (*Dableh v Ontario Hydro* (1996), 68 CPR (3d) 129, at 149).

[147] In the context of applications under the *Regulations*, the mere sale of the patented product by a second person is not sufficient. "Something more" is required (*Sanofi-Aventis Canada Inc v*

Apotex Inc, 2006 FCA 357, at para 18 [*Sanofi (2006)*]). That "something more" is "something active [that] must be done" by the inducing party (*Pfizer Canada Inc v Apotex Inc*, 2005 FC 1421, at para 167). It is not sufficient for the first person to simply demonstrate that the second person recognized that "off label" prescription by doctors, dispensation by pharmacists, and subsequent consumption by patients would occur (*Aventis Pharma Inc v Apotex Inc*, 2005 FC 1461, at para 32 [*Aventis (2005 FC 1461)*]; aff'd, *Sanofi (2006)*, above; *Sanofi (2007)*, above; *Sanofi-Aventis Canada Inc v Laboratoire Riva Inc*, 2008 FC 291, at para 31).

(v) *Analysis*

(a) The first prong of the tri-partite test

[148] During the hearing of this application, the initial and principal focus of the parties with respect to the '626 Patent was upon the second prong of the tri-partite test for inducement, namely, whether the PM for the Generic Drug is likely to influence physicians or pharmacists to prescribe or dispense the Generic Drug to patients for neuroprotection. Accordingly, I will only deal briefly with the first prong of that test now.

[149] In the context of an NOC proceeding, the first prong of the tri-partite test for assessing inducement to infringement is whether infringement is *likely* to occur if an NOC is issued (*Abbott Laboratories Ltd v Canada (Minister of Health)*, 2007 FCA 251, at paras 26-27; *Aventis Pharma Inc v Pharmascience Inc*, 2006 FCA 229, at para 60); *AB Hassle v Canada (Minister of National Health and Welfare)*, [2002] 3 FC 221, at para 69). In cross-examination, Dr. Parkinson stated that the Generic Product will be prescribed by physicians (and used by patients) for neuroprotection, based on Sandoz's PM, the Krupin article and his clinical experience. For the reasons discussed in Parts IV.C and IV.D of these reasons below, I prefer Dr. Parkinson's evidence on this issue and on

the related issue of whether brimonidine actually confers neuroprotection on patients, to the evidence provided by Dr. Jampel and Dr. Mitra.

[150] Based on Dr. Parkinson's evidence, I am satisfied that Allergan has demonstrated, on a balance of probabilities, that the Generic Drug is likely to be used for neuroprotection, and therefore is likely to infringe, the '626 Patent.

(b) The second prong of the tri-partite test

[151] Allergan's position that Sandoz will induce infringement of the '626 Patent is based on one sentence that appears in Sandoz's PM and one reference that appears towards the end of the list of references that are included at the end of that PM. Specifically, at page 23 of the PM, under the heading *Animal Pharmacology*, Sandoz stated the following:

> When the action of brimonidine tartrate as a neuroprotective agent was evaluated *in vitro* and *in vivo* pharmacological studies in rats, no deleterious effects on the optic nerve were observed.

[152] In addition, the ninth in a list of 13 references at the back of the PM is a reference to an article by Mr. Lai, one of the named inventors of the '626 Patent, and several other employees of Allergan, entitled "Neuroprotective effect of ocular hypertension agent brimonidine" (the "Lai Article").The first sentence in the Summary that appears at the outset of the Lai Article states: "The ocular hypotensive agent brimonidine has been shown to be neuroprotective in a mechanical insult model of the optic nerve." After briefly discussing certain data obtained from an *in vivo* study of rat retinal RNA and from an *in vitro* study of rat hippocampal neuronal culture, the Summary states: "These data suggest that brimonidine is an effective ocular hypotensive agent with neuroprotective properties." Under the heading "Results and Conclusions," the Lai Article stated: "After 15 days of [BID] topical dosing, mRNA of retinal bFGF increased 50% (0.5% brimonidine) and 200% (1%

brimonidine) above control (Fig. 2). Sufficient amount of brimonidine appeared to have reached the retina to induce retinal bFGF upregulation." The Lai Article proceeded to conclude as follows:

> Present findings that brimonidine can upregulate bFGF in retina suggests a mechanistic basis for neuroprotection. Brimonidine is a unique ocular hypotensive drug since it lowers IOP by both decreasing the aqueous humor production and increasing uveoscleral outflow. The added neuroprotective properties of brimonidine in the retina will present a [sic] new opportunities to explore in neuroprotection in the eye.

[153] Allergan submitted that if Sandoz receives the NOC that it seeks, it will be permitted to disseminate its PM to doctors and pharmacists in Canada, who in turn will be influenced by the above quoted sentence that appears at page 23 of the Sandoz PM and/or the Lai Reference (collectively the "Neuroprotective Information") to prescribe or dispense the Generic Drug to patients for the neuroprotective use claimed by the '626 Patent. Allergan maintained that the presence of the Neuroprotective Information in Sandoz's PM is the "something more" contemplated by the jurisprudence.

[154] For the reasons set forth below, I disagree. Stated alternatively, I have concluded that the second prong of the tri-partite test described under the preceding heading above has not been met.

[155] Accordingly, the principal question that remains is whether ophthalmologists and pharmacists will in fact be influenced by the Neuroprotective Information to prescribe or dispense, respectively, the Generic Drug for neuroprotection, as required by the second prong of the test.

[156] Sandoz attempted to minimize the potential significance of the Neuroprotective Information in its PM by noting that it does not appear in the "Indications and Clinical Use" section of the PM.

Among other things, that section of the PM describes the indications of the Generic Drug as follows:

> Sandoz Brimonidine/ Timolol (brimonidine tartrate 0.2%/timolol maleate as timolol 0.5%) ophthalmic solution is indicated for the control of intraocular pressure in patients with chronic open-angle glaucoma or ocular hypertension who are insufficiently responsive to IOP reducing monotherapy AND when the use of Sandoz Brimonidine/ Timolol is considered appropriate. Sandoz Brimonidine/ Timolol is also indicated for reduction of long-term fluctuation in IOP. In addition to controlling IOP, Sandoz Brimonidine/ Timolol reduces long-term variability, or fluctuation, in IOP. Together, reductions in IOP and in IOP fluctuation are expected to slow the progression of visual field loss in patients with glaucoma.

[157] However, I agree with Prothonotary Tabib's conclusion, reached earlier in these proceedings in connection with a motion for the production of Sandoz's entire PM, that "several decisions of this Court support the proposition that in determining whether an allegation that a second person will not infringe or induce infringement of a patent directed to the use of the medicine, the Product Monograph in its entirety is a key document." See: *Allergan Inc v Sandoz Canada Inc* (June 21 2010), Ottawa T-154-10 (Federal Court) (Tabib P), citing *Aventis Pharma Inc v Apotex Inc*, 2005 FC 1381; *AB Hassle v Genpharm Inc*, 2003 FC 1443; *Sanofi (2007)*, above.

[158] In his initial affidavit, Dr. Parkinson focused on Allergan's now abandoned theory of inducement, described at paragraph 130 above. He did not mention the theory of inducement now being advanced by Allergan. Nor did he mention the Neuroprotective Information in Sandoz's PM. However, he did state the following:

> Canadian ophthalmologists have access to and when they see fit can access generic product monographs on Health Canada's website or by obtaining paper copies which are available on demand. Canadian ophthalmologists, including the POSITA, would be able to read,

> understand and apply the totality of the reported studies and information taught in Sandoz's proposed product monograph, and where they need information to make prescribing decisions they can and do consider the totality of the relevant information referred to in the monograph. (Emphasis added.)

[159] In his second affidavit, Dr. Parkinson focused on replying to various statements made in Dr. Jampel's affidavit, particularly with respect to the validity of the '626 Patent. Once again, Dr. Parkinson did not mention the theory of inducement now being advanced by Allergan, or the Neuroprotective Information in Sandoz's PM.

[160] In cross-examination, Dr. Parkinson was challenged on his opinion regarding the manner in which ophthalmologists use PMs. He explained that "when a clinician uses a drug, it is incumbent upon them [*sic*] to understand and to have read the entire monograph, it is not just the first two paragraphs [Indications and Clinical Use]. And contained elsewhere in [Sandoz's PM] is evidence that this drug has neuroprotective qualities, and that's why we use this section." He then referred to the Neuroprotective Information in Sandoz's PM , and stated: "and I read that, as a clinician, that as noted deleterious effects were observed in the optic nerve in these rats that this agent has conferred some neuroprotective qualities on those nerves." There was nothing in the balance of his cross-examination that was particularly helpful in assisting me to make a determination with respect to Allergan's position that Sandoz's PM will induce infringement of the '626 Patent.

[161] On balance, I am prepared to accept that at least some ophthalmologists read a product's PM before prescribing that product. That said, I did not find Dr. Parkinson's opinion on this point to be particularly compelling. As a result, I will not attach determinative weight to that opinion in assessing whether Allergan has met its burden of demonstrating that Sandoz's allegation of non-infringement is not justified.

[162] Turning to Dr. Jampel, he acknowledged in cross-examination that he did not review the list of references in Sandoz's PM, and that therefore he was not aware, when he prepared his affidavit, that the Lai Article was contained in that list. He also conceded that (i) he was not aware that the word "neuroprotective" appeared in Allergan's PM for COMBIGAN, which was attached as exhibit G to his affidavit, and (ii) he did not know what COMBIGAN is approved for in the U.S. This suggests that he is at least one practicing ophthalmologist who does not read the entire PM filed in respect of a product, before prescribing that product.

[163] Dr. Jampel also conceded that he had never read a Canadian PM before the case at bar and that he had no particular knowledge with respect to how Canadian ophthalmologists use PMs. Nevertheless, I find some of his evidence regarding how Canadian ophthalmologists are likely to use Sandoz's PM to be helpful.

[164] In particular, with respect to the Neuroprotection Information that appears in a single sentence at page 23 of Sandoz's PM, he stated: "A physician who read this cold would have no idea what they're talking about." When asked if his opinion on this point would change if the sentence was read in light of Lai Article, he replied that physicians likely would understand it to be referring to the experiments described in the Lai Article. However, he also characterized the "crush model of optic nerve injury" upon which the *in vivo* experiment described in the Lai Article was based, to be "a crude and early relationship to looking at glaucoma." As to the *in vitro* experiment described in the Lai Article, he characterized it as involving "[c]ultured rat cells in a dish" and stated that it would not be considered to constitute "an animal study." In any event, he stated that "the drug reps who come by never mention animal studies" and suggested that physicians would not be particularly interested in information from "animal models of neuroprotection."

[165] In addition, Dr. Jampel stated that the Lai Article would not be considered to be the type of study or reference contemplated by section 4.6 of Health Canada's publication entitled *Guidance For Industry - Product Monograph*. Section 4.6 states that the references section of a PM "should include a selection of the pivotal clinical studies that formed the basis for the evaluation of the drug and the studies highlighted in the Clinical Trial section … [and] may also include references to the best published papers containing preclinical data on the drug and selected, authoritative papers concerning the use of the drug." Dr. Jampel stated that the Lai Article is neither such a pivotal clinical study nor a published paper containing preclinical data on the drug in question. However, he acknowledged in cross-examination that one of the reasons why the Lai Article may have been included in the list of references at the back of Sandoz's PM is "possibly" to elucidate a mode of action of brimonidine in neuroprotection. In addition, he acknowledged that one of the reasons why animal data may be included in a monograph is to provide physicians with extra information about a particular type of use.

[166] Dr. Jampel also noted that COMBIGAN is not indicated for neuroprotection and that Sandoz's PM does not include neuroprotection as one of the indications for the Generic Drug. He added that there is nothing in Sandoz's PM or the COMBIGAN PM that mentions the use of brimonidine to provide neuroprotection in humans, and nothing in those documents which states that brimonidine has a neuroprotective effect. (The sentence on page 23 of Sandoz's PM simply observes that "no deleterious effects on the optic nerve [of the rats studied] were observed.")

[167] After considering the foregoing and the other evidence and submissions made by the parties, I have determined that Allergan has not met its burden of establishing, on a balance of probabilities, that ophthalmologists or pharmacists likely would be influenced by the Neuroprotective Information in Sandoz's PM to prescribe or dispense the generic drug for neuroprotection. Notwithstanding Dr.

Parkinson's evidence and the adverse inference that I draw from the fact that Sandoz appears to have consciously chosen to leave the Neuroprotective Information in its PM, I am not persuaded that the Neuroprotective Information (i) constitutes the "something more" required by the jurisprudence, or (ii) is anything more than "a mere reference to the new use" described in the '626 Patent (*Sanofi (2007)*, above, at para 9; *Aventis (2005 FC 1461)*, above, at paras 32-36, aff'd *Sanofi (2006)*, above).

[168] Allergan was not able to identify any case in which information that was as limited as the Neuroprotective Information, and that was subject to the various shortcomings identified by Dr. Jampel, provided the basis for a finding that a generic drug manufacturer's allegation of non-infringement was not justified.

[169] Although Allergan suggested that Sandoz would be free to "market" the Generic Drug for neuroprotection, I am not persuaded, on a balance of probabilities, that on the particular facts of this case this is likely to occur, particularly having regard to (i) Dr. Jampel's uncontradicted evidence that representatives of drug companies do not generally mention animal studies and that physicians would not be particularly interested in information from "animal models of neuroprotection", (ii) the Generic Drug is not indicated for neuroprotection, and (iii) the marketing of a drug for unapproved uses is prohibited (*Goodridge v Pfizer Canada Inc*, 2010 ONSC 1095, at para 15).

[170] Based on all of the foregoing, I am satisfied that Allergan has not met its burden in these proceedings to establish the second prong of the three-prong test that must be met to establish infringement of a use claim by inducement.

(c) The third prong of the tri-partite test

[171] The Neuroprotective Information in Sandoz's PM also appeared in the PM that Allergan filed with respect to COMBIGAN. Indeed, the two PMs are virtually identical. That said, Sandoz deleted from its PM a small number of passages that appeared in Allergan's PM, as well as six of the articles in the list of references that appeared at the back of Allergan's PM. Sandoz did not offer any explanation of why, having taken the trouble to delete certain material from Allergan's PM, it retained the Neuroprotective Information. In my view, in the absence of such an explanation, this raises an inference that Sandoz retained the Neuroprotective Information in its PM for the purposes of influencing ophthalmologists and pharmacists to prescribe and dispense, respectively, the Generic Drug for the neuroprotective use claimed by the '626 Patent. Based on this inference, I conclude that the third prong of the aforementioned tri-partite test for establishing infringement of a use claim by inducement has been established on a balance of probabilities.

C. Are Sandoz's allegations of non-infringement of the claims in the '626 Patent justified?

[172] Sandoz is alleging that the Generic Drug will not infringe any of the claims in the '626 Patent for the following two reasons:

i. COMBIGAN is not approved for a neuroprotective use; and

ii. the Generic Drug will not be used for neuroprotection.

[173] With respect to the first of these two arguments, Sandoz noted that Dr. Parkinson admitted in cross-examination that there is nothing in the PM for COMBIGAN that mentions neuroprotection in humans. Based on that acknowledgment on behalf of Allergan, Sandoz submitted that it cannot be "early-working" the purported invention of the '626 Patent, and that it cannot be infringing the

"patented invention" of the '626 Patent. It added that this proceeding as it relates to the '626 Patent ought to be dismissed for this reason alone.

[174] I disagree. As Allergan noted, Sandoz's position on this point confuses the safety approval regime under the Regulations with the law set forth in the *Patent Act*, RSC 1985, c P-4. An allegation of non-infringement cannot be justified solely on the basis that the first person's PM for the patented product does not mention a particular use of the product that the second person has admitted is within the scope of the claims of the patent. In the case at bar, Sandoz's own construction of the '626 Patent is that it claims "a purported new use of certain compounds, including brimonidine … 'to inhibit or prevent nerve cell injury or death … for protecting the retinal or optic nerve cells in a mammal suffering a noxious action or at risk of experiencing a noxious action on said nerve cells.'." The fact that COMBIGAN is not yet approved for neuroprotection does not mean that there is no "quid quo pro," as suggested by Sandoz. The "quid" that Allergan provided in exchange for the '626 Patent was the disclosure of its invention, which was set forth in the patent. *Biolyse Pharma Corporation v Canada (Attorney General)*, 2005 SCC 26, [2005] 1 SCR 533, is distinguishable, as "the Biolyse product was properly treated as an innovator drug rather than a copy-cat drug" (para 34) and it "was *not* approved on the basis of bioequivalence with the BMS product embodying its inventions" (para 54). Moreover, the Biolyse product was based on paclitaxel that was extracted from a different species of yew than the paclitaxel that was the subject of BMS's patents covering new formulations and methods of administration of the paclitaxel, but not the paclitaxel itself.

[175] Turning to the allegation that the Generic Drug will not be used for neuroprotection, Sandoz stated that: (i) COMBIGAN is not approved for use as a neuroprotective agent, (ii) the Generic Product will not be approved for use as a neuroprotective agent, (iii) Allergan did not adduce any

"infringement evidence" that provides any support for its contention that patients would "use" the Generic Product "for neuroprotection," and (iv) an article published earlier this year (the "Krupin Article") can have no relevance to the approved uses of COMBIGAN and does not support Allergan's position that patients will use the Generic Product for neuroprotection.

[176] I am satisfied that Allergan has demonstrated, on a balance of probabilities, that this allegation of non-infringement is not justified.

[177] Sandoz's arguments regarding the approved uses of COMBIGAN and the proposed uses of the Generic Product have already been addressed in my reasons above and do not need to be revisited.

[178] As to the suggestion that the Krupin Article was not adduced as part of Allergan's "infringement evidence," it was published after Allergan filed that evidence and was properly put before the Court as an appendix to Dr. Parkinson's second affidavit. That affidavit was filed in accordance with Prothonotary Tabib's Order regarding the parties' evidence with respect to validity. Dr. Parkinson's affidavit properly addressed the evidence that Sandoz adduced to support its allegations of invalidity. One of Sandoz's allegations of invalidity is an allegation of lack of utility, which is based on some of the same arguments that Sandoz is advancing to support this particular claim of non-infringement. Accordingly, I reject the suggestion that the Krupin Article is not properly before the Court on this non-infringement issue.

[179] The Krupin Article reported the results of a four-year double-masked, randomized, multicenter clinical trial of the efficacy of monotherapy with brimonidine (0.2%) versus timolol (0.5%) eyedrops in preventing or delaying visual field progression in patients with low-pressure glaucoma. In his affidavit, Dr. Parkinson stated that the ophthalmic community had been awaiting

the results of this study, because it was designed to be large enough to address the concerns that had been identified by Ms. Meredith Saylor in an article published in April 2009. The latter article (the "Saylor Article") reported on the research that had been performed to date, but did not discuss any new research.

[180] Dr. Parkinson observed that, by limiting their study to patients with low-pressure glaucoma, the authors of the Krupin Article (collectively, "Krupin") were able to separate the effect of lowering high IOP from the neuroprotective effect of brimonidine. He also noted that, by comparing brimonidine with timolol, which has a similar IOP lowering effect as brimonidine, Krupin was able to measure the neuroprotective effect of brimonidine that is separate from any benefit that may have been achieved by a reduction of IOP in patients with normal IOP.

[181] The Krupin Article described the results of the study in the following terms:

> In summary, in this randomized clinical trial, twice-daily treatment with topical brimonidine tartrate 0.2% preserves visual field better than treatment with topical timolol maleate 0.5% in a subset of open-angle glaucoma patients with statistically normal IOP. Given the similar IOP-lowering efficacy of the 2 compounds, this finding is consistent with a non-IOP related mechanism of action favoring brimonidine-treated patients. The effectiveness of brimonidine in delaying or preventing visual field progression has to be judged in context of brimonidine's adverse event profile, primarily localized external ocular allergy. Validation of a neuroprotective mechanism of action requires additional basic science and clinical research <u>to confirm</u> the present results prior to altering current clinical patient care paradigms. (Emphasis added.)

[182] Dr. Parkinson stated in his affidavit that the Krupin study "demonstrates that the topical administration of brimonidine to patients has a neuroprotective effect by a mechanism unrelated to the effect of brimonidine on IOP." He proceeded to add:

> [I]t is my opinion that brimonidine is useful as a neuroprotective agent. Brimonidine protects the retinal or optic nerve cells in a mammal suffering a noxious action or at risk of experiencing a noxious action. Brimonidine inhibits and prevents nerve cell injury or death. Dr. Jampel's statements to the contrary are not correct.

[183] When it was suggested to him, during cross-examination, that "the best current knowledge is that it has not yet been proven that brimonidine has a neuroprotective effect," Dr. Parkinson said he "totally" disagreed. When further pressed, he stated: "[t]he word confirm there is very, very potent and very important." (Emphasis added.) He elaborated as follows: "I read that as [saying] that they're just encouraging others to corroborate their results, as any good researcher should and would do." He rejected the suggestion that the conclusion of the Krupin Article should be interpreted as suggesting that "maybe it's not true" that brimonidine has a neuroprotective effect in humans. He also characterized the results of the Krupin study as being "very positive," and observed that "[t]here never stops being a question in medicine."

[184] Elsewhere during his cross-examination, Dr. Parkinson was asked what he was relying upon to support his statement that brimonidine is a neuroprotective agent that is administered by eyedrops today. He replied: "I'm relying on the [COMBIGAN] product monograph as well as the Krupin paper as well as my clinical experience."

[185] When asked, during re-examination, how his clinical experience influenced his view that the Generic Product would be used for neuroprotection, Dr. Parkinson stated that his clinical experience is often one of the most important considerations for him. In this regard, he stated:

> [My clinical experience] is that when all else fails and we've got the [IOP] at an extremely low level and there is still progression, that in some patients, and it's not all, but in some patients, having that

> patient exposed to … [brimonidine] seems to give them the benefit, and enhanced stability.

[186] Dr. Parkinson proceeded to state that one of the reasons why he and some of his colleagues were so happy to see the results of the Krupin study is that brimonidine is "a tool that we use in patients who are losing vision in spite of very low eye pressure" (emphasis added).

[187] Dr. Parkinson was also asked to comment on the acknowledgment at page 8 of the Krupin Article that "it remains possible that another, not yet described timolol or brimonidine-related vascular (or other) phenomenon could account for the results of the present study." He replied as follows:

> To me, reading this as a clinician, this -- personally, that gives me sort of -- allows me to give more credence to this article because they say that. Because, of course, as I said in the past, this is just one article. The results show that there is certainly an effect, but they are – they're wise enough -- I'm going to use that word -- to say look, you know, we always have to be on the lookout for other effects, and let's not discount that. So I respect that. (Emphasis added.)

[188] Dr. Jampel's affidavit was written before he had seen the Krupin Article. At paragraph 87 of his affidavit, Dr. Jampel stated:

> Topical administration of brimonidine does not do what the 626 patent promises - topical brimonidine does not protect the retinal or optic nerve cells in humans. Topical application of brimonidine does not confer the neuroprotection promised by the 66 patent.

[189] In cross-examination, Dr. Jampel was asked whether he would concede, now that he had seen the results of the Krupin study, that he may not have been correct to assert unequivocally in his affidavit that brimonidine does not have a neuroprotective effect. He replied: "I would not write that today."

[190] Dr. Jampel also conceded that the design of the Krupin study "seemed acceptable" and that it passed peer review. That said, he maintained that "this study presents some highly aberrant results that need to be explained." In this regard, he referred to "the absence of an [IOP] lowering effect of either the brimonidine or the timolol." He questioned that particular result of the study because ophthalmologists have prescribed brimonidine and timolol to a large number of patients for the purpose of lowering eye pressure. That said, he acknowledged that the Krupin study is "suggestive" of a neuroprotective effect.

[191] On balance, I prefer Dr. Parkinson's evidence on this issue of whether the Generic Drug is likely to be used for neuroprotection. In my view, Dr. Parkinson stood up very well to his cross-examination. His testimony was very credible and more persuasive than Dr. Jampel's. I believe him when he stated that he and other ophthalmologists do in fact prescribe brimonidine for neuroprotection. His testimony on this point had an "air of reality" to it, which was reinforced by the following response that Dr. Parkinson gave earlier in his cross-examination. When pressed about why an ophthalmologist would prescribe brimonidine for neuroprotection on the basis of the animal data reported in the Lai Article, he replied:

> Sometimes you do things in medicine to help patients and to help patients on an individual basis, and that's how you treat patients, one patient at a time. And with, specifically, this topic, neuroprotection, in a horrible disease like glaucoma where we don't have an agent other than this drug that can strengthen an optic nerve, we are treating a disease by lowering eye pressure. This is our only other treatments for glaucoma.
>
> So when patients are worsening or they're -- or you see their vision failing, you may do things that as long as they're doing no harm to the patient, you may do them. And if you see effects clinically that possibly are backed up by animal studies, you're going to continue to do them because that's what's right for the patient. And that's how medicine is practiced, sir.

[192] Based on all of the foregoing, I conclude that Allergan has met its burden of demonstrating, on a balance of probabilities, that Sandoz's allegations of non-infringement of the '626 Patent are not justified.

D. *Sandoz's allegations of invalidity of the '626 Patent*

[193] Sandoz alleges that the '626 Patent is invalid for inutility, on the basis that:

i. the claims therein cover non-useful subject matter; and

ii. the utility of that subject matter could not be soundly predicted as of the priority date and the Canadian filing date of the '626 Patent.

(a) *The Utility of the subject matter of the '626 Patent*

[194] Some of the evidence regarding the utility of the subject matter of the '626 Patent was discussed in the immediately preceding section above. It is not necessary to repeat that evidence in connection with the issue of utility. I will simply discuss the additional evidence that is relevant to my assessment of that issue.

[195] In his affidavit, Dr. Jampel referred to a number of studies that were reported upon in the Saylor Article, for the purpose of supporting his opinion that the topical application of brimonidine does not confer the neuroprotection promised by the '626 Patent.

[196] The Saylor Article was published in April 2009, and reviewed the evidence that existed at that time with respect to the neuroprotective qualities of brimonidine in optic nerve and retina injury. It did not report on any new research.

[197] At the outset of that article, it was noted that "recent experimental and animal models suggest a neuroprotective effect of brimonidine." It was observed that "[t]hese investigations

indicate that [brimonidine] might have therapeutic effects if used clinically to treat optic neuropathies in humans." Later in the article, the authors stated: "[s]everal experimental animal models demonstrated the neuroprotective effects of topically and systemically administered brimonidine in reducing the effects of optic nerve injury …"

[198] However, after reviewing the reports of various clinical trials that had been conducted to assess brimonidine as a potential treatment in humans, the authors concluded that "the achievements in animal models regarding the neuroprotective effects of brimonidine in treating ischemic optic nerve injury have not translated into effective clinical applications."

[199] In his affidavit, Dr. Jampel noted that some of the clinical trials reviewed in the Saylor Article related to brimonidine as a potential treatment for nonarteritic anterior ischemic optic neuropathy (NAION), which is a condition thought to be caused by an acute impairment of the blood supply to the optic nerve. Dr. Jampel observed that the Saylor Article reported that those trials suggest that brimonidine treatment has failed to demonstrate neuroprotective efficacy in humans. Dr. Jampel made a similar observation with respect to certain clinical trials involving other optic neuropathy conditions, which were reported upon in the Saylor Article. In addition, he noted that in a more recent review (the "Chau Article"), the authors reported a similar finding with respect to their study of brimonidine as a neuroprotective in three small human clinical trials.

[200] In addition to the foregoing, Dr. Jampel stated in his affidavit that "[t]opical administration is not identified as a route of administration for the neuroprotective agents of the 626 Patent." In support of this opinion, Dr. Jampel noted that, under the heading *Summary of the Invention*, the '626 Patent describes the new method for protecting the optic nerve and retina of the mammalian eye, as comprising "administering to the mammal either systemically or by intrabulbar injection an

effective amount" of brimonidine. He added that "[t]here is nothing in the 626 Patent to indicate that the inventors considered topical administration of brimonidine to be a method of administration that confers the purported neuroprotective effects."

[201] In replying to Dr. Jampel, Dr. Parkinson noted (in his second affidavit) that, when Dr. Jampel discussed what the Saylor Article had to say about the aforementioned clinical trials regarding NAION, he omitted to note the following passage that immediately preceded the passage to which he referred:

> Even in the absence of controlled clinical trials, physicians prescribed brimonidine and α agonists as treatment for NAION. This perhaps stems from the substantial experimental evidence demonstrating the efficacy of brimonidine as a neuroprotective agent in animal models of ischemia.

[202] Dr. Parkinson added that this observation is consistent with the practice of Canadian ophthalmologists, who do in fact prescribed brimonidine for patients for the treatment of NAION. In this regard, he stated: "I have personally prescribed brimonidine for the treatment of NAION. In my experience, brimonidine has helped to stabilize my patients after the initial insult and has prevented some degree of vision loss that might otherwise have occurred."

[203] In addition, Dr. Parkinson noted that the Saylor article reported that, in a 2006 study by Wilhelm and others, "[t]here seemed to be a slight nonsignificant improvement in visual fields for the treatment group compared with the control group." He further noted that the Saylor Article observed that the results of that study were inconclusive. With respect to Leber hereditary optic neuropathy, he observed that the Saylor Article reported that "a non-significant trend was found, suggesting slower progression of visual field loss in eyes treated with topical brimonidine (0.2%)." He stated that this suggests that brimonidine is effective at treating Leber hereditary optic

neuropathy, although he acknowledged that the results of the study are not statistically significant because only 17 patients were used in the study. He added: "far from reporting that brimonidine is not effective, Ms. Saylor's conclusion is that additional studies are required (but may be difficult to construct)." Despite the limitations of the studies reviewed in the Saylor Article, he repeated that brimonidine has been administered to patients for the treatment of NAION, as well as for Leber hereditary optic neuropathy.

[204] In cross-examination, Dr. Parkinson conceded that, as of April 2009, when the Saylor Article was published, the utility of brimonidine as a neuroprotective agent "was a question mark." He also agreed that the Saylor Article would be another piece of evidence that the POSITA would use in determining whether or not brimonidine has any neuroprotective effects in humans. When asked if he would agree that the Krupin study is no more than one piece of evidence, he replied that its significance should not be minimized in that way, because one has to look at the study's methods, its results, and how the patients and the data were treated. He added: "what's most important in this is you have to decide if it -- if it makes sense and if it jibes with your clinical impression, making very -- making sure not to unfairly bias the paper in either way."

[205] With respect to whether the '626 Patent includes topical administration of brimonidine within its scope, Dr. Parkinson made several observations. First, he noted that Sandoz made no allegation in its NOA that topical administration of brimonidine is not within the claims of the '626 Patent. However, I am satisfied that this allegation was indeed made in paragraph 96 of the NOA, which states: "With respect to claims 7-9, 11, 27-29 and 31, Sandoz additionally does not infringe these claims as Sandoz Brimonidine/Timolol will be administered as an eye-drop solution. Sandoz Brimonidine/Timolol will not be administered orally, intramuscularly, or by intrabulbar injection in the eye."

[206] Dr. Parkinson then disagreed with Dr. Jampel's position on this point. In this regard, he observed that there is no limiting language about the route of administration in any of claims 1, 2, 14, 20 or 21 of the '626 Patent. He added: "The POSITA reading the '626 Patent as of the day it was published (January 16, 1997) would understand that the inventors did not exclude the topical administration of brimonidine from the claims in that the topical administration was a possible route of administration for the invention claimed" in the aforementioned claims. In addition, he noted that at pages 2 and 3 of the '626 Patent, the inventors discussed a study that showed brimonidine to be effective in reducing intraocular pressure in rabbits, cats and monkeys after topical administration to the eye. He further supported his position by observing that (i) the patent states that the mode of administration and the dosage regimen is left to the judgment of the treating physician, and (ii) the patent specifically states that "[c]onventional modes of administration and standard dosage regimens of protective agents … can be used", and (iii) the "POSITA would have been well aware that topical administration was a conventional mode of administering ophthalmic drugs as of January 16, 1997."

[207] After carefully considering all of the foregoing, including the information discussed in Part IV.C above, I find Dr. Parkinson's evidence to be more credible and persuasive than Dr. Jampel's evidence on the issue of whether Sandoz's allegation that brimonidine is not useful for neuroprotection is justified. I accept Dr. Parkinson's testimony that (i) he and other ophthalmologists do in fact prescribe brimonidine for neural protection for the treatment of NAION, Leber hereditary optic neuropathy and glaucoma, and (ii) the Krupin study "demonstrates that the topical administration of brimonidine to patients has a neuroprotective effect by a mechanism unrelated to the effect of brimonidine on IOP."

[208] Based on Dr. Parkinson's evidence and the Krupin study, I am satisfied that Allergan has met its burden of demonstrating, on a balance of probabilities, that this allegation made by Sandoz is not justified.

[209] Contrary to Sandoz's position, Allergan is not required to unequivocally demonstrate that topically applied brimonidine has no neuroprotective effect. It is sufficient for Allergan to demonstrate, on a balance of probabilities, that there is at least a "mere scintilla" of utility (*Eli Lilly*, above, at para 76). In my view, Allergan has more than met its burden in this regard.

(b) *Was the subject matter of the '626 Patent soundly predicted?*

[210] In its written submissions in this proceeding, Sandoz asserted that the animal testing disclosed in the '626 Patent did not provide a sufficient basis for the alleged inventors of that patent to soundly predict that the topical application of the test compounds, let alone brimonidine, would have any neuroprotective effect in humans. Sandoz added that the '626 Patent fails to disclose any articulable and sound line of reasoning for such a prediction.

[211] In support of its assertions, Sandoz noted that the two examples discussed in the '626 Patent involved an *in vitro* test using cultures from nerves of a portion of rat brains, and an *in vivo* test in which live rats were subjected to dissection of the optic nerve that was then injured. Sandoz further noted that the test compounds did not include brimonidine and were injected intraperitoneally (into the abdomen). Sandoz also repeated that there was no topical administration specifically mentioned anywhere in the '626 Patent, and no examples provided involving the administration of any compounds to humans or testing using human cells.

[212] Allergan began its reply to the foregoing by noting that Sandoz did not allege in its NOA that the inventors named in the '626 Patent did not have any basis to predict that topically

administered brimonidine would be neuroprotective in humans. Allergan took the position that this allegation by Sandoz should therefore not be considered in this proceeding.

[213] I agree. Sandoz's allegations with respect to a lack of sound prediction of the subject matter of the '626 Patent were contained in the following three paragraphs of its NOA:

> 135. In addition to only testing one known compound, the patentee only tested two different types of methods that create the alleged "injury" to the optical nerve cells: glutamate toxicity, and "a nerve crush model of mechanical injury" (page 9, line 1). However the patentee claims that Formula I compounds protect from any "noxious action" (claims 1, 2 and 20, 21 and claims dependent therefrom). Further, the patentee fails to disclose that any of the particular claimed "noxious actions" (at claims 3-6; 15-19; 22-26) create optical nerve damage that is in any way similar to the damage created by putting a toxicity, or mechanical nerve crush.
>
> 136. For example, it was understood that glutamate may result in one mode of cell injury and glaucoma (Quigley, 1995). The patentee has failed to demonstrate that all noxious actions will create a similar mode of cell injury.
>
> 137. The claims are therefore invalid as covering subject matter whose utility could not be soundly predicted as of the priority date, and also the Canadian filing date of the 626 patent (in the event the court determines the filing date to be the relevant date, which Sandoz alleges is not the correct date).

[214] In my view, it is readily apparent from the foregoing quoted text that Sandoz did not make any allegation with respect to whether the disclosure in the '626 Patent provided a basis to soundly predict that topically administered brimonidine would be neuroprotective in humans. Accordingly, Sandoz is precluded from raising this argument in the current proceeding.

[215] In the event that I am found to have erred in reaching this conclusion, I will proceed below to address Sandoz's position on its merits.

[216] The doctrine of sound prediction has three components, namely:

i. there must be a factual basis for the prediction;

ii. at the filing date of the patent application, the inventor must have had an articulable

iii. and sound line of reasoning from which the desired result can be inferred from the factual basis; and

iv. there must be proper disclosure.

(See: *Apotex Inc v Wellcome Foundation Ltd*, [2002] 4 SCR 153, at para 70 [*Wellcome*].)

[217] In *Sanofi*, the Supreme Court confirmed that a sound prediction does not require certainty and that there is a "public-interest in early disclosure of new and useful inventions even before their utility has been fully verified by tests" (*Sanofi*, above, at para 105). However, more than "a lucky guess or mere speculation" is required (*Wellcome*, at para 69). In short, "a sound prediction requires a *prima facie* reasonable inference of utility" (*Eli Lilly*, above, at para 85).

[218] Dr. Jampel's opinion that the disclosure in the '626 Patent did not provide the POSITA with the basis to soundly predict that topically administered brimonidine would have a neuroprotective effect in humans was based on three considerations. First, the test compounds used in the *in vivo* study disclosed in Example 2 of the patent were injected into the abdomen of the rats, rather than topically administered into the rats' eyes. Second, there is no discussion of topical administration of any compound in the patent. Third, prior to June 1996, there had been no demonstration of brimonidine or any other agent providing neuroprotection in humans, and the animal testing

reported in the '626 Patent "was not sufficient to show the topical application of the test compounds, let alone brimonidine, had any neuroprotective effects."

[219] For the reasons previously discussed, I accept Dr. Parkinson's opinion that the topical administration of brimonidine was contemplated by, and is within the scope of, the '626 Patent. I also accept Dr. Parkinson's evidence that a drug which enters the eye reaches the retinal or optic nerve cells in one of two ways, namely, (i) through the systemic blood circulation system, which brings a topically administered drug to the eye in the same way as a drug administered via injection, and (ii) diffusion inside the eye. Both Dr. Jampel and Dr. Mitra agreed with this evidence. Dr. Jampel further agreed that the POSITA would have been aware of this systemic affect of brimonidine in 1995. Taken together, the foregoing negates the first two of the considerations relied upon by Dr. Jampel in reaching his opinion.

[220] Therefore, the key question that remains is whether the '626 Patent disclosed the factual basis on which a POSITA could soundly predict in June 1996 that the topical administration of brimonidine would have a neuroprotective effect in humans, once the invention was reduced to practice (*Merck & Co Inc v Apotex Inc.*, 2010 FC 1265, at para 521 [*Merck (2010 FC 1265)*]).

[221] In *Wellcome*, the factual basis for the sound prediction of a new use compound rested upon the results of an *in vitro* test of AZT against the HIV in a human cell line along with the inventor's data on AZT, including animal tests. The line of reasoning was found to be the inventor's knowledge of the mechanism for reproduction of a retrovirus (*Wellcome*, above, at para 72; *Eli Lilly*, above, at para 85).

[222] Likewise, in the case at bar, the factual basis for the sound prediction was provided by the two examples with corresponding data that were disclosed in the '626 Patent. Notwithstanding the

fact that the experiments did not involve human cells, Dr. Parkinson relied on the affirmative findings of a neuroprotective activity in rats to conclude that "[t]he POSITA would understand that the data disclosed made it highly likely that brimonidine would have some level of efficacy as a neuroprotective agent in humans." I found this evidence to be more persuasive and credible than Dr. Jampel's opinion on this point.

[223] In my view, this line of reasoning, which was also disclosed in the '626 Patent, is *prima facie* reasonable and entirely sound, particularly given that the test compounds made their way to the rats' eyes through the bloodstream, a fact that was not contested. In short, it was known that, when brimonidine is topically administered, some of it enters the systemic bloodstream. The experiments disclosed in the patent demonstrated that, when introduced into the systemic bloodstream, the compounds of Formula 1, which include brimonidine, reached the rats' eyes and provided a neuroprotective effect on the rats' optic nerves. Finally, Dr. Parkinson provided persuasive expert evidence that a POSITA would understand from the results of those experiments that it was highly likely that brimonidine would have some level of efficacy as a neuroprotective agent in humans. In addition, Dr. Parkinson's evidence that physicians often use animal data as a basis upon which to treat their patients was not contradicted.

[224] My conclusion in this regard is reinforced by (i) the fact that Dr. Jampel conceded in cross-examination that the experiments disclosed in the '626 Patent demonstrated that brimonidine did in fact have a neuroprotective effect in rats, and (ii) one of the studies disclosed in the '626 Patent was an *in vivo* study involving the optic nerves of a mammal. In this latter regard, Sandoz did not dispute Allergan's contentions that (i) *in vivo* animal studies can often provide a much more sound basis upon which to predict an effect in humans, than *in vitro* studies involving human cells, and (ii) *in vivo* animal studies have been found to provide a sufficient basis upon which to soundly predict a

particular effect on humans (see, for example, *Pfizer Canada Inc v Canada (Minister of Health)*, 2007 FCA 209, at para 153, another case that involved *in vivo* rat studies). Indeed, *in vitro* animal studies have also been found to be sufficient in this regard (see, e.g., *Merck (2010 FC 1265)*, above, at paras 506-511).

[225] I am also satisfied that the disclosure in the '626 Patent is sufficiently fulsome and clear. I note that the parties did not make any specific representations on this third requirement of the doctrine of sound prediction.

[226] Based on the foregoing, I have no hesitation in concluding that Allergan has satisfied its burden of demonstrating, on a balance of probabilities, that Sandoz's allegation that the '626 Patent did not soundly predict that the topical administration of brimonidine would have a neuroprotective effect in humans is not justified.

V. Conclusion and Disposition

[227] For the reasons set forth above, I have concluded that Allergan has demonstrated, on a balance of probabilities, that Sandoz's allegations with respect to the invalidity of the '764 Patent and the invalidity of the '626 Patent are not justified.

[228] With respect to infringement of the '626 Patent, I have concluded that Allergan has failed to demonstrate that Sandoz's PM for the Generic Product is likely to induce infringement of the '626 Patent. However, in the event that I am found to have erred in reaching this conclusion, I have concluded that Allergan has met its burden of demonstrating, on a balance of probabilities, that Sandoz's other allegations of non-infringement are not justified.

JUDGMENT

THIS COURT'S ORDERS AND AJUDGES that:

1. This application is granted in part, with costs.

2. Pursuant to subsection 6(2) of the *Regulations*, the Minister is prohibited from issuing a Notice of Compliance to Sandoz in respect of the drug described in Sandoz's Product Monograph dated October 7, 2009 (Sandoz Brimonidine/Timolol) until after the expiry of Canadian Letters Patent No. 2,440,764.

3. Allergan's application for a prohibition order, until the expiry of Canadian Letters Patent No. 2,225,626, is dismissed.

"Paul S. Crampton"
Judge

FEDERAL COURT

SOLICITORS OF RECORD

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APPEARANCES:

Andrew J. Reddon Steven G. Mason Steven Tanner	FOR THE APPLICANTS
David Rieve Angela Furlanetto Ryan Evans	FOR THE RESPONDENT SANDOZ CANADA INC.

SOLICITORS OF RECORD:

Andrew J. Reddon Steven G. Mason Steven Tanner	FOR THE APPLICANTS
Myles J. Kirvan Deputy Attorney General of Canada	FOR THE RESPONDENT THE MINISTER OF HEALTH
David Rieve Angela Furlanetto Ryan Evans	FOR THE RESPONDENT SANDOZ CANADA INC.