Federal Court  Cour fédérale

Date: 20231218

Docket: T-1994-21

Citation: 2023 FC 1686

Ottawa, Ontario, December 18, 2023

PRESENT: Mr. Justice Pentney

BETWEEN:

ALLERGAN, INC. AND ABBVIE CORPORATION

Plaintiffs

and

JUNO PHARMACEUTICALS CORP.

Defendant

PUBLIC JUDGMENT AND REASONS
(Confidential version issued on December 13 2023)

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I. Introduction

[1] This is a patent infringement action pursuant to s. 6(1) of the *Patented Medicines (Notice of Compliance) Regulations*, SOR/93-133 [*PM(NOC) Regulations*].

[2] The patent at issue concerns a drug used to treat glaucoma and intra-ocular hypertension ("IOH"). Glaucoma is sometimes called the "silent thief of sight" because it slowly damages the eyes and can cause irreparable harm before there is any vision loss. Pressure inside of the eye, known as intra-ocular pressure ("IOP"), is a leading cause of glaucoma; it can damage the optic nerve at the back of the eye, and once that occurs the loss of sight is permanent. Ocular hypertension describes a condition in which a person's IOP is above the normal range but they have not been diagnosed with glaucoma or have no detectable damage.

[3] Although there is no cure for glaucoma or ocular hypertension, there are some treatments that can slow or stop the condition. To be effective, such treatment must generally begin before the patient is aware of any loss of vision.

[4] The Plaintiffs own a patent for a product marketed as LUMIGAN RC that was launched in 2009 and is used to treat glaucoma and ocular hypertension by lowering the pressure inside the eye, referred to as intraocular pressure ("IOP"). LUMIGAN RC is an improvement over a previous formulation (LUMIGAN .03; hereafter "Old LUMIGAN") that was successful in lowering IOP but had unwanted side effects.

[5] The Defendant seeks to obtain approval for a generic equivalent to the Plaintiffs' LUMIGAN RC. The Defendant concedes that its product would infringe the LUMIGAN RC patent, but argue that the patent is invalid for obviousness and insufficient disclosure. The Plaintiffs seek to prevent the Defendants from entering the market with their generic drug formulation.

[6] Previous decisions of this Court and the Federal Court of Appeal under the prior regime found the Plaintiffs' patent to be valid and prevented the entry into the market of generic equivalents. In addition, there has been litigation about the equivalent patent in both the United States and the United Kingdom. The question of whether those decisions are relevant to the current proceeding under the new *Patented Medicines (Notice of Compliance) Regulation* ("PM(NOC)") regime is one of the issues raised in this case.

[7] At trial, only two claims of the patent remained in issue, and the parties focused most of their attention on the question of obviousness.

[8] For the reasons that follow I find in favour of the Plaintiffs. The Patent is not invalid for obviousness or lack of sufficient disclosure. The Plaintiffs are entitled to the declaration they seek.

II. Background

A. *The Parties*

[9] The Plaintiffs are Allergan Inc. (“Allergan”) and AbbVie Corporation. Allergan is an innovative pharmaceutical company incorporated under the laws of Canada.

[10] Allergan (Canada) filed submissions in Canada seeking Notices of Compliance (“NOC”) in respect of LUMIGAN RC (bimatoprost ophthalmic solution 0.01% w/v) for the treatment of elevated IOP in patients with open angle glaucoma or ocular hypertension. Subsequently, Allergan Canada amalgamated with the plaintiff AbbVie Corporation (“AbbVie”), and on September 9, 2022, the NOC for LUMIGAN RC was updated to reflect the amalgamation and now lists AbbVie as the NOC holder. Accordingly, under the *PM(NOC) Regulations*, AbbVie is a “first person.”

[11] Allergan (United States) is the owner of Canadian Patent No. 2,585,691 (“the 691 Patent”) which is in issue in this litigation. For ease of reference, AbbVie and Allergan (Canada and US) are referred to in these reasons as “Allergan”.

[12] Juno Pharmaceuticals Corp. (“Juno”) is a pharmaceutical company located in Ontario. It develops and sells generic drug products. Juno filed an Abbreviated New Drug Submission (ANDS) with Health Canada seeking approval of Juno’s 0.01% w/v bimatoprost solution for ophthalmic administration (the Juno Product) for the treatment of elevated IOP in patients with

open angle glaucoma or ocular hypertension. For the purposes of its ANDS, Juno compared the Juno Product to LUMIGAN RC to demonstrate bioequivalence.

[13] As required by the *PM(NOC) Regulations*, Juno delivered a Notice of Allegation (NOA) relating to the 691 Patent to AbbVie on November 19, 2021. Juno is therefore a "second person" under the *Regulations*.

B. *The 691 Patent*

[14] The 691 Patent is titled "Enhanced Bimatoprost Ophthalmic Solution." Its claim date is March 16, 2005. Its publication date is September 28, 2006. The patent expires on March 14, 2026.

[15] Allergan alleges that Juno will infringe claims 16 and 19 of the 691 Patent:

> 16. A composition comprising by weight 0.01% bimatoprost, 0.02% benzalkonium chloride, 0.268% sodium phosphate dibasic heptahydrate, 0.014% citric acid monohydrate, 0.81% sodium chloride, water, and wherein said composition is an aqueous liquid with a pH adjusted to 7.3.
>
> 19. Use of a composition according to any one of claims 1 to 16 for treating glaucoma or intraocular hypertension in a mammal.

[16] Claim 19 is a dependent claim that refers, *inter alia*, to Claim 1. Because this was raised by the Defendant as an issue in the trial, it is convenient to reproduce Claim 1 here:

> 1. A composition comprising from 0.005% to 0.02% bimatoprost by weight and from 0.01% to 0.025% by weight

> benzalkonium chloride, wherein said composition is an aqueous liquid which is formulated for ophthalmic administration.

[17] As noted earlier, LUMIGAN RC was developed because of issues regarding the old LUMIGAN product. Although old LUMIGAN was effective in lowering IOP, it caused a condition called conjunctive hyperemia, which is characterized by redness in the eye, itching and eye pain. The condition was serious enough that a significant number of patients stopped taking the medication. (Old LUMIGAN also caused some other side effects such as lengthening of the eyelashes which was a problem for people who wear glasses, but these are not relevant for this case). Allergan therefore sought to develop a formulation that was similarly effective in lowering IOP but did not cause the unwanted side effects.

[18] The new formulation discovered by Allergan involved two key changes from the formula for the old LUMIGAN product: a significant reduction in the amount of bimatoprost (the active ingredient) combined with a significant increase in the amount of benzalkonium chloride ("BAK"), the preservative used in both products. This is key to understanding the issues in this case, and the table set out below provides a useful summary:

Product	Bimatoprost	BAK
Old LUMIGAN	0.03% (300 ppm)	0.005% (50 ppm)
LUMIGAN RC	0.01% (100 ppm)	0.02 % (200 ppm)

Ppm = parts per million

C. *Previous Litigation Concerning the 691 Patent*

(1) Litigation in Canada

[19] The 691 Patent has been the subject of litigation under the prior PM(NOC) regime in this Court and the Federal Court of Appeal: see *Allergan Inc v Canada (Health)*, 2014 FC 567 [*Apotex FC*]; *Apotex Inc v Allergan Inc*, 2015 FCA 137 [*Apotex FCA*]; and see the companion case *Allergan Inc v Canada (Health),* 2014 FC 566 [*Cobalt FC*].

[20] Under the prior PM(NOC) regime, a patent holder would bring an application in this Court to prohibit the Minister of Health from issuing a NOC to a generic drug manufacturer to prevent the allegedly patent-infringing product from entering the market. The case was then dealt with under the *Federal Courts Rules,* SOR/98-106 that govern applications. This meant that evidence was tendered by affidavit, and the usual discovery process applicable to actions launched by statement of claim was not available.

[21] The two decisions of this Court, *Apotex FC and Cobalt FC* (by Justice James O'Reilly), are very similar, and so I will only summarize the *Apotex FC* decision, which involved an application for a NOC by Apotex, a generic pharmaceuticals company. In response to Allergan's application, Apotex alleged that the 691 Patent was invalid on the grounds of obviousness, lack

of utility and anticipation. Justice O'Reilly found in favour of Allergan and issued the prohibition order, thus preventing Apotex (and Cobalt Pharmaceuticals Company in the companion case) from entering the market. He accepted Allergan's argument that the inventive concept of the 691 Patent included comparable efficacy to old LUMIGAN, and found that the new formulation involved inventive steps and was not obvious.

[22] After reviewing the evidence and arguments on the issues, Justice O'Reilly found that Apotex had not met its burden of showing that the 691 Patent was invalid, and so he issued the order of prohibition requested by Allergan.

[23] Apotex appealed, and the Federal Court of Appeal, in a short judgment, dismissed the appeal: *Apotex FCA*. For our purposes, two findings are relevant. The Court of Appeal found that there was no error in the construction of the 691 Patent or in the determination of the inventive concept adopted by Justice O'Reilly. Justice Eleanor Dawson for the Federal Court of Appeal found:

> [7] Dealing with each asserted error, I am satisfied that:
>
> > i. The Federal Court did not err in its construction of the inventive concept of the 691 patent. The nub of Apotex' argument is that the Federal Court inferred the inventive concept from data found in the 691 patent. In Sanofi, at paragraph 77, the Supreme Court found that the inventive concept of the claims there in issue was not readily discernible from the claims themselves. It was therefore acceptable to read the specification in the patent to construe the inventive concept. In the present case, the relevant claims related to a chemical composition and the use of the composition for treating glaucoma or intraocular hypertension in a mammal. The Federal Court found the composition claimed did not determine the claims' inventive concept and so it construed the inventive concept by reading the patent as a whole. In doing

> so, the Federal Court considered the inventive concept in light of the disclosure of the patent from the viewpoint of the skilled reader. This was not an error of law and no palpable and overriding error has been shown in the Federal Court's conclusion as to the inventive concept.
>
> (*Citing Apotex Inc v Sanofi-Synthelabo Canada Inc*, 2008 SCC 61, [2008] 3 SCR 265 [*Sanofi*].)

[24] The Federal Court of Appeal's specific finding on inventive concept, and its relevance, if any, to the current proceeding is discussed below, and so I will not say more about it here.

(2) Litigation in Other Countries

[25] In addition to the prior Canadian cases, Allergan holds an equivalent patent in other countries, which has been litigated in the United Kingdom and United States.

[26] In the case brought in the United Kingdom, the Court found that the patent was obvious, and therefore invalid: *Allergan Inc v Aspire Pharma Ltd*, [2019] EWHC 1085 (Pat); leave to appeal from this decision was denied.

[27] On the other hand, in the United States the challenge was dismissed because the court found the patent was not obvious: *Allergan Inc v Sandoz Inc*, No 6:11-cv-00441 (ED Tex Jan 1, 2014), and this decision was upheld on appeal by the Federal Circuit Court of Appeal: *Allergan Inc v Sandoz Inc*, No 14-1275 (Fed Cir 2015).

[28] In my view, nothing can be gained by a review of these decisions, because they are based on different facts assessed under different legal frameworks. Therefore no more need be said about them here.

D. *Glaucoma, Intraocular Hypertension, & the Challenge of Creating Effective Eye Drops*

[29] Glaucoma is a chronic, progressive and incurable disease of the eye in which IOP is elevated. Left untreated, or if not treated effectively, glaucoma causes gradual, irreversible vision loss and can ultimately lead to total blindness. Almost 70 million people suffer from glaucoma, which is the second leading cause of blindness worldwide. It affects up to 2% of the total population, and up to 4% of people over age 75.

[30] As noted above, glaucoma is frequently called the “silent thief of sight” because patients with the condition do not experience any symptoms before significant vision loss occurs, and so they are not aware of what they are losing until it is gone. That presents a challenge because patients must begin daily treatment to stop the condition from advancing before they notice any problems with their vision, and for some the treatment can seem worse than the condition.

[31] Intraocular hypertension (IOH) and glaucoma are part of the same disease continuum. Patients diagnosed with glaucoma have suffered detectable damage to their optic nerves, nerve fiber layers and/or visual fields. Patients with IOH have elevated IOPs but no detectable damage to their optic nerves or nerve fiber layers, and no loss of their normal visual fields. Left uncontrolled, or inadequately controlled, ocular hypertension can cause damage to the optic nerve resulting in visual field loss, i.e. glaucoma.

[32] Higher than normal IOP causes damage to the optic nerve, which is the pressure-sensitive part of the eye. This nerve is the connection between the eye and the brain. High IOP causes damage to the nerve over time, so while the eye itself may be functioning, only some or none of the signals reach the brain. Glaucoma is diagnosed when the optic nerve is damaged, causing some loss of vision.

[33] The challenge of effective treatment involves confronting issues of physiology as well as the psychology of human behaviour. The first difficulty with treating ophthalmic conditions using eye drops comes down to a simple fact: effective treatment involves getting drugs into the eye, but the eye is very well designed to keep things out. A second challenge involves human nature: patients may stop using eye drops that cause discomfort or disagreeable side effects because they find the treatment can seem worse than the disease.

(1) The Physiology of the Eye

[34] The human eyeball is a slightly asymmetrical sphere that is composed of several primary layers (see Figure 1 below).

[35] The anatomy of the eye includes:

(a) **Cornea:** The eye's front surface (a clear dome over the iris), the cornea covers the iris, pupil, and anterior chamber. The cornea is responsible for approximately 70% of the total focusing ability of the eye;

(b) **Iris:** Located behind the cornea, is the colored part of the eye and contains the pupil. The iris adjusts the size of the pupil to control the amount of light entering the eye;

(c) **Pupil:** The black circle within the eye's iris. The pupil's size determines how much light enters the eye;

(d) **Lens:** Located behind the pupil, the lens focuses light on the retina;

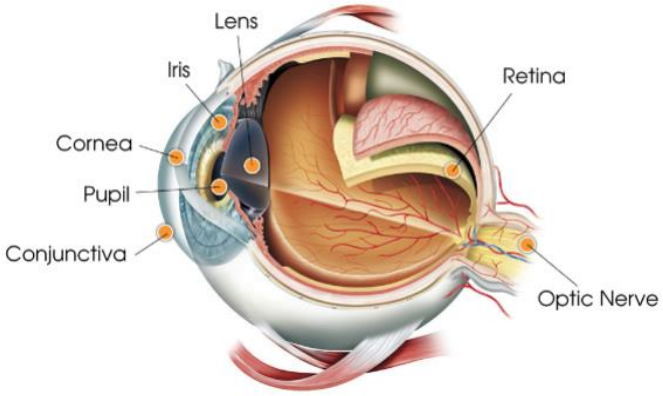
(e) **Sclera:** The white of the eye;

(f) **Conjunctiva:** A thin clear mucous membrane that covers the outer surface of the sclera and lines the inner surfaces of the eyelids;

(g) **Retina:** Located at the back of the eye, receives images from the cornea and the lens and contains light-sensitive cells, called photoreceptors; and

(h) **Optic Nerve:** Transports visual signals from the retina in the back of the eye to the brain.

Figure 1



[36] The eyeball has three chambers of fluids. The anterior chamber is located in the front of the eye between the cornea and the iris. The areas in front of the lens on either side of the iris are filled with aqueous humour produced by the ciliary body, a ring of tissue that encircles the lens. The front portion of the eye does not have its own blood vessels and the aqueous humour provides nutrition, oxygen and antioxidants to that part of the eye. The posterior chamber is behind the iris but in front of the lens). The vitreous chamber is located in the centre of the eye behind the lens and in front of the retina.

[37] Glaucoma and ocular hypertension are characterized by elevated IOP, caused by an imbalance in the inflow and outflow of aqueous humour. In a healthy eye, the aqueous humour leaves the eye primarily by the trabecular meshwork and canal of Schlemm, from which it goes into systemic circulation. The conventional pathway accounts for much of the aqueous humour outflow. An alternative pathway is the uveoscleral route, in which the aqueous humour flows through the ciliary muscles and eventually into the choroid and sclera. Up to 30% of the outflow may follow this alternative route.

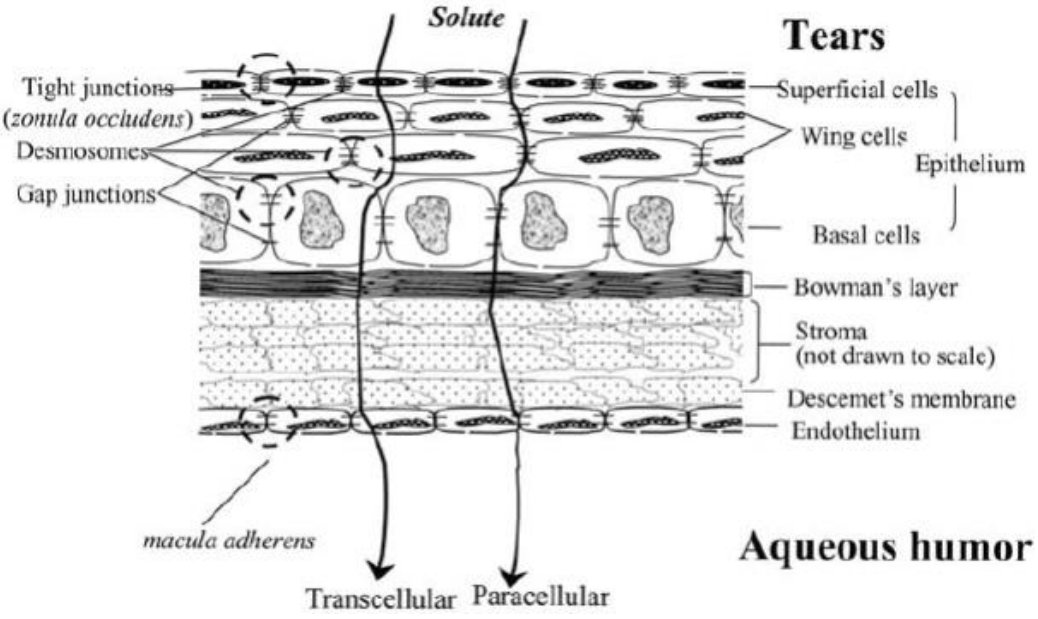
[38] The basic problem with glaucoma and ocular hypertension is that the eye's drainage mechanisms do not allow aqueous humour fluid to flow out of the eye rapidly enough, which results in a rise in IOP. This is understood to be caused by degeneration of the trabecular meshwork. Because the inflow and outflow are not in balance, IOP increases which can cause damage to the optic nerve leading to disturbance of the visual field, and eventually total blindness.

[39] As with all medications, part of the effective treatment of a condition using eye drops involves getting the right amount of the active ingredient – the drug – to the right place and for the right amount of time. In the treatment of glaucoma and ocular hypertension, this involves getting the drug to penetrate the eyeball so that it can have the desired effect of lowing IOP.

[40] Very little of the active ingredient in an eye drop will be able to penetrate the eye. The experts testified that only 1% to 10% of a medication will get into the eye. As anyone who has ever had a speck of grit get into their eye will appreciate, the involuntary blinking and increased tear production reaction that if triggered can be a very effective way of flushing foreign substances or objects from the eye. The same thing can happen when administering an eye drop.

[41] The next barrier to getting the active ingredient inside the eyeball is the design of the eye itself. Topically applied ophthalmic drugs enter the eye through the cornea, the sclera and/or the conjunctiva. The cornea is the transparent ocular membrane that covers the front of the eyeball. The cornea is comprised of five layers. The outermost layer is the corneal epithelium, which is the eye's primary barrier against the entry of foreign substances. This layer is comprised of many corneal epithelial cells packed tightly together in a unique arrangement called "tight junctions" (see Figure 2 below). This makes it difficult for foreign substances to penetrate the eye, unless they can penetrate the epithelial cells or are small enough to squeeze through the tight junctions.

Figure 2



[42] Behind the corneal epithelium are the Bowman's layer, the stroma, the Descemet's membrane, and the endothelium. To reach the interior of the eye via the cornea, a drug must pass through each of these layers. There are two ways in which a drug can do that. The first, called transcellular transport, involves the drug passing directly through the cells of each layer (i.e. enter a cell and exit out the other side, and then again through the next four layers of cells). The second, called paracellular transport, involves the drug squeezing between the small spaces in between the cells of each layer.

[43] The route that a drug takes to penetrate the eye depends on how the drug behaves in the presence of either water or lipids. Drugs that have an affinity for lipids are referred to as "lipophilic"; drugs that have an affinity for water are referred to as "hydrophilic". It is more

accurate to describe drugs as more or less lipophilic or hydrophilic, since these qualities are on a spectrum.

[44] The corneal epithelium is lipophilic, or oily, a bit like the outer layer of our skin. This serves to keep water from penetrating the eye, which would disturb our vision and cause an imbalance in the IOP. Lipophilic drugs can pass more easily through the epithelial cell layer, because lipids have an affinity for lipids. Drugs that have an affinity for watery (hydrophilic) environments will have a more difficult time penetrating the eye because water and lipids repel each other.

[45] Once a lipophilic drug has penetrated the cornea, it faces another hurdle because the stroma is more hydrophilic and will thus tend to repel the drug. Drugs with an affinity for water will pass through this layer more easily.

(2) The Challenge of Human Behaviour

[46] The second major challenge associated with using eye drops to treat glaucoma or ocular hypertension is patient “compliance” (also referred to as “adherence”). No matter how well a medication may perform in the lab, it will not be an effective treatment if patients will not use it on a consistent basis. This is particularly important for glaucoma and ocular hypertension, for two reasons.

[47] First, as noted earlier, these conditions can progress and cause irreparable damage before the patient experiences any symptoms or otherwise becomes aware of the harm. Eye drops can

slow or halt the progression of the condition by lowering IOP, but that requires the patient to start and continue the treatment even though they are not experiencing any problems. In that circumstance, one can understand why difficulties associated with taking the medication as prescribed – for example because it requires multiple daily doses, causes stinging or other discomfort when administered, or it results in unpleasant side effects – can lead patients to discontinue using it. As one expert testified at the trial, some patients may find the treatment worse than the disease, ignoring the longer-term consequences of their choice.

[48] Second, daily compliance with the treatment regime is especially important, because although fluctuations in IOP during the day occur naturally, studies have shown that wide variations in IOP can accelerate or increase the harm to the eyesight of patients with glaucoma or ocular hypertension. As one of the experts said, taking glaucoma medication is boring, because it requires a daily dose of one or more medications, often for the rest of a person's life. And the patient will usually not notice any improvement in their vision, because the medication is actually only stopping further decline.

[49] With this background we turn to the issues and analysis of the matters in dispute.

III. Issues

[50] There are only two issues in this case:

A. Is the 691 Patent invalid due to obviousness?

B. Is the 691 Patent invalid for insufficient disclosure?

[51] Juno concedes that its generic drug will infringe the 691 Patent. The focus of the evidence and arguments was on Juno's arguments about invalidity.

IV. Witnesses

[52] There was no real challenge to any of the experts' qualifications, but the parties made submissions regarding the weight that should be accorded to their evidence. I set out an overview of the experts' backgrounds and my overall credibility findings here; more detail is provided on specific points in the analysis of the issues in dispute in subsequent sections of the decision.

A. *Allergan's Witnesses*

(1) Dr. Noecker

[53] Dr. Robert Noecker is a practicing ophthalmologist and Assistant Clinical Professor of Ophthalmology at the Yale School of Medicine, as well as a Clinical Professor at the Frank Netter School of Medicine at Quinnipiac University. He also currently serves as Director of Glaucoma at Ophthalmic Consultants of Connecticut. He obtained his MD from the University of North Carolina's School of Medicine in 1990 and completed his residency in ophthalmology in 1994. In total, he has over 30 years of experience studying and treating glaucoma and ocular hypertension.

[54] Dr. Noecker has expertise in the design and conduct of clinical trials and has participated in over 40 funded clinical trials, the majority related to glaucoma drugs, including LUMIGAN®, TRAVATAN®, and XALATAN®. He has also published over 100 peer-reviewed publications,

with a particular focus on glaucoma, including on the efficacy and safety of bimatoprost and the use of the preservative BAK in ocular formulations. In 2005, on the priority date of the 691 Patent, Dr. Noecker was the Vice-Chair of the UPMC Eye Center at the University of Pittsburgh. He testified that he was treating about 200 glaucoma patients per week at that time.

[55] Dr. Noecker was qualified as an expert on the following terms:

> Dr. Robert Noecker is an ophthalmologist with expertise in treating patients with glaucoma and ocular hypertension, including the efficacy and safety of bimatoprost and other compounds that lower intraocular eye pressure ("IOP lowering agents"). Dr. Noecker's expertise also includes the design and conduct of clinical trials involving ophthalmic medicines, including IOP lowering agents. Dr. Noecker is an expert in the evaluation of preservatives used in ophthalmic solutions, including their safety and efficacy.

[56] Juno argued that Dr. Noecker's evidence should be given less weight because he has "extensive and ongoing" ties to Allergan, having received research funding from the company since the 1990's and because he has previously testified as an expert witness for Allergan. In addition, Juno submits that his evidence was marred by contradictory statements and an apparent lack of knowledge on certain key details. For example, they point out that Dr. Noecker's description of the findings of a key research study was incorrect, and thus Juno contends that his evidence should not be relied upon.

[57] Overall, I found Dr. Noecker's evidence to be clear and consistent, and he displayed an understanding of this role as an expert witness in the proceeding. In regard to Juno's argument about his ties to Allergan, I was attentive to possible bias and did not perceive any.

[58] Juno's challenge to Dr. Noecker's evidence is discussed below, in particular the mistake he made in his expert report regarding a key piece of prior art. On this, Dr. Noecker readily acknowledged his error, and his expert report correctly referred to the document in another section. I do not find that this mistake diminishes his overall credibility.

[59] Dr. Noecker is clearly familiar with the various medications used for treating glaucoma and IOH at the relevant time based on his extensive clinical experience at that time, and he has written articles that directly address the key questions in dispute in this case. It should be noted that Juno's experts cited Dr. Noecker's research in their own reports. As discussed below, I give Dr. Noecker's evidence substantial weight in analysing the key issues in dispute.

(2) Dr. Berkland

[60] Dr. Cory Berkland is a pharmaceutical formulation scientist with expertise in ophthalmic pharmaceutical formulations. He received his PhD from the University of Illinois, Department of Chemical and Bimolecular Engineering. He currently holds the title of Solon E. Summerfield Distinguished Professor at the University of Kansas in the Department of Pharmaceutical Chemistry and the Department of Chemical Engineering. He has been teaching at the University of Kansas since 2005 and his teaching includes material on ocular drug delivery.

[61] Dr. Berkland also leads the Berkland Lab at the University of Kansas, which works on the interface of medicine and engineering in drug development. He is the CEO of a number of start-up companies developing ocular therapies and drugs. Dr. Berkland has published approximately 200 peer-reviewed papers, including on pharmaceutical formulation and ocular

drug delivery systems. His expertise includes drug development, drug delivery, and the transport of drugs across biological membranes, including the corneal epithelium.

[62] Dr. Berkland was qualified as an expert on the following terms:

> Dr. Cory Berkland is a pharmaceutical formulation scientist with expertise in ophthalmic drug delivery, including pharmaceutical formulations for ophthalmic application and their ingredients. His expertise includes drug development, drug delivery, and the transport of drugs across biological membranes, including the corneal epithelium. His expertise also includes design, development, and evaluation of ophthalmic drug delivery systems to administer drugs to the eye including in animal studies.

[63] Juno argued that Dr. Berkland revealed himself to be a witness lacking in independence, and they say he provided evasive testimony and refused to make concessions that other witnesses readily made. They point to inconsistent testimony on important matters, and argue that his review of the prior art was tainted by hindsight.

[64] Overall, I found Dr. Berkland to be a credible expert witness. His evidence was clear and consistent and he demonstrated a capacity to provide objective assistance to the Court, as required of an expert witness.

(3) Dr. Chang (Inventor)

[65] Dr. Chin-Ming Chang is an inventor of the 691 Patent. Dr. Chang earned a PhD in Pharmaceutics from the University of Texas in 2005. He began his employment with Allergan in 1999 on the Formulation Development Team as a Senior Scientist. In 2003, he was promoted to

Principal Scientist on this team. Dr. Chang was the lead formulator for Allergan's Lumigan Enhancement Team (which eventually developed LUMIGAN RC) from 2003 until the completion of the project. He no longer works for Allergan.

[66] Juno argued that Dr. Chang's evidence was incomplete, because he was not part of the Lumigan Enhancement Team from the beginning of the work. Therefore, he could not testify from personal experience about the earliest stages of the work that resulted in the development of LUMIGAN RC. Juno questioned why Allergan did not choose a fact witness who was part of the team during the entire period of work.

[67] Overall, I found Dr. Chang to be a credible witness, who acknowledged the limitations of his testimony. He testified in a forthright manner, and his evidence was not seriously challenged on cross-examination. I acknowledge the truth of Juno's assertion that he did not have personal knowledge of the earlier phases of the team's work. Given the documents that have been produced, and the unchallenged evidence that the first two years of effort did not produce a clinically viable alternative product, nothing turns on this issue.

B. *Juno's Witnesses*

(1) Dr. Morgan

[68] Dr. James Edward Morgan is a practicing ophthalmologist and clinical scientist at the University Hospital of Wales. He has also been Professor of Ophthalmology at Cardiff University since 1997. He has over 25 years of experience working in the field of ophthalmology

with a specialized research interest in glaucoma. In 2005, Dr. Morgan was the consultant in charge of glaucoma services in Cardiff, working as a front-line clinician treating patients with glaucoma.

[69] Dr. Morgan has authored or co-authored over 109 peer-reviewed journal articles. He currently serves on the editorial board of *The Journal of Glaucoma*. He works in a clinical setting ten hours per week providing care to glaucoma patients and sees approximately 100 patients per month.

[70] Dr. Morgan was qualified as an expert on the following terms:

> Dr. James Edwards Morgan is a medical doctor and specialist in ophthalmology with expertise in treating patients with glaucoma and conditions of elevated intraocular pressure ("IOP"), including the efficacy and safety of drugs used for the treatment of glaucoma and high IOP. Dr. Morgan is also a clinical scientist with a specialized research interest in glaucoma. He leads clinical glaucoma studies and provides direct patient care including glaucoma services. Dr. Morgan's expertise includes the design and evaluation of ophthalmic therapies, as well as the detection, causes, prevention, and treatment of glaucoma and associated conditions, including in human and animal studies.

[71] Allergan argued that Dr. Morgan's publications and research interests do not pertain to matters directly relevant to the case, and that his clinical experience is much more limited than that of Dr. Noecker. Allergan also asserts that Dr. Morgan's answers were often evasive, and that his expert report was tainted by his failure to mention highly relevant prior art, as well as his omission of key facts.

[72] Overall, I found Dr. Morgan's evidence to be of limited utility. Dr. Morgan described himself as a "clinician scientist", but his limited clinical experience with glaucoma was evident from his lack of familiarity with some relevant glaucoma medications. He has also not studied or published on subjects directly relevant to the issues in this case. As regards his understanding of his duties as an expert witness, while I found Dr. Morgan to be genuine in his desire to be of assistance to the Court, I was troubled by certain of his answers for reasons set out in more detail below.

[73] As discussed below, while I give Dr. Morgan's evidence some weight, I found his evidence to be of limited usefulness on the key points in contention.

(2) Dr. Alany

[74] Dr. Raid Ghassan Alany is a pharmaceutical formulator who received his PhD in ocular drug delivery from the University of Otago, New Zealand, in 2001. He joined the faculty of the University of Auckland's newly created Pharmaceutics program in 2001. In 2011, Dr. Alany joined the Kingston University, London, in the United Kingdom, as Professor of Pharmaceutics.

[75] Since 2017, Dr. Alany has been Professor of Pharmaceutical Formulation and Drug Delivery. His research relates mainly to ophthalmic drug deliver. He is on the Editorial Board of numerous journals in the subjects of pharmaceutics and drug delivery and a Section Editor for the journal *Clinical and Experimental Ophthalmology* on the subject of ocular pharmacotherapy.

[76] Dr. Alany was qualified as an expert on the following terms:

> Dr. Raid Ghassan Alany is a pharmaceutical formulator with expertise in ophthalmic drug delivery, including ophthalmic formulations and their ingredients, precorneal retention and clearance studies, ocular bioavailability and pharmacodynamic studies, ocular irritation and tolerability and tear film stability studies. Dr. Alany's expertise also extends to the preparation, design, development, manufacture, and evaluation of ophthalmic drug delivery systems, including in human and animal studies.

[77] Allergan submits that Dr. Alany's credibility was seriously undermined during cross-examination, in particular because his description of the Common General Knowledge ("CGK") in this case materially differed from his expert evidence in the United Kingdom patent case involving LUMIGAN RC. They argue that his evidence was selective, including his one-sided presentation of the benefits of BAK as a preservative and penetration enhancer, while ignoring its cytotoxic effects and the ample literature suggesting that its use should be avoided or minimized.

[78] Overall, I found Dr. Alany's credibility as an expert witness to be significantly diminished because he did not provide forthright, careful and objective evidence in areas relating to his expertise. Instead, his evidence was heavily weighted in favour of Juno's position in the litigation. He did not mention that his evidence on the CGK of the Skilled Formulator as of March 2005 was so different in the United Kingdom case until this was pointed out to him in cross-examination. When challenged, he did not respond in a forthright manner but rather sought to dispute the point – despite the evidence that resoundingly confirmed it. His evidence about what formed CGK at the relevant time included many references that can only properly be considered as part of the state of the art. Parts of his testimony were also confusing, and he often spoke to matters that fall within the expertise of a skilled ophthalmologist.

[79] As discussed below, I give Dr. Alany's evidence little weight in the analysis of the key issues.

V. The Skilled Person

[80] Since patents and their claims are directed at "persons of skill in the art" ("POSITA"), the Court must construe a patent from the perspective of the POSITA: *Sanofi* at para 67.The POSITA is a hypothetical person possessing the ordinary skill and knowledge of the particular art to which the invention relates and a mind willing to understand a specification that is addressed to them (*Free World Trust v Électro Santé Inc*, 2000 SCC 66 [*Free World Trust*] at para 44, cited in *Tetra Tech EBA Inc v Georgetown Rail Equipment Company*, 2019 FCA 203 at para 25).

[81] The skilled person is understood to be a technician skilled in the art but having no scintilla of inventiveness or imagination; a paragon of deduction and dexterity, wholly devoid of intuition; a triumph of the left hemisphere over the right (*Sanofi* at para 52). The POSITA may be conceived of as a team of people possessed of different skills (see *Janssen Inc v Pharmascience Inc*, 2022 FC 1218 at para 112, citing *Teva Canada Limited v Janssen Inc*, 2018 FC 754 at paragraph 66, aff'd 2019 FCA 273).

[82] There was no real dispute between the parties that the POSITA, in regard to the 691 Patent, consists of a team comprised of an ophthalmologist and a formulator.

[83] The Skilled Ophthalmologist would have completed an MD degree as well as a residency program in ophthalmology, and would have experience treating patients with glaucoma and ocular hypertension. Indeed, the evidence indicates that most ophthalmologists spend a great deal of their professional lives helping patients with these conditions.

[84] The Skilled Formulator would have a Master's degree in science or engineering relating to the preparation of pharmaceutical formulations, as well as a few years of experience preparing formulations; in the alternative, the Skilled Formulator would have a PhD in one of those same fields and would have acquired experience in preparing pharmaceutical formulations in the course of their training. The Skilled Formulator would have experience in preparing formulations for ophthalmic administration (i.e. eye drops).

VI. Claim Construction

[85] The first step in a patent suit, before assessing validity or infringement – is to construe the claims: *Whirlpool Corp v Camco Inc*, 2000 SCC 67, [2000] 2 SCR 1067 [*Whirlpool*] at para 43. This step requires the interpretation of the patent "to ascertain the nature of the invention and methods of its performance" and "to understand what was meant by the words in the claims" (*Tearlab Corporation v I-MED Pharma Inc*, 2019 FCA 179 [*Tearlab Corporation*] at para 33, citing *Consolboard Inc v MacMillan Bloedel (Sask) Ltd*, 1981 CanLII 15 (SCC), [1981] 1 SCR. 504 [*Consolboard*] at 520). As previously stated, claim construction is done from the perspective of the POSITA.

[86] There was no dispute between the parties on the question of claims construction. Despite their agreement, claims construction remains a question of law for me to determine (*Whirlpool* at para 76); *Tearlab Corporation* at para 28). In this case, the exercise is quite straightforward.

A. *Legal Principles*

[87] The general principles of claim construction are now well established, based on the three leading Supreme Court of Canada decisions: *Whirlpool* at paras 49-55*; Free World Trust* at paras 31-67*; Consolboard* at 520.

[88] The Federal Court of Appeal summarized these principles in *Tearlab Corporation*:

> [32] To identify these elements, the claim language must be read through the eyes of a [person of skill in the art (POSITA)], in light of the latter's common general knowledge (*Free World Trust* at paras. 44-45; see also *Frac Shack* at para. 60; *Whirlpool* at para. 53). As noted in *Free World Trust*:
>
> > [51] …The words chosen by the inventor will be read in the sense the inventor is presumed to have intended, and in a way that is sympathetic to accomplishment of the inventor's purpose expressed or implicit in the text of the claims. However, if the inventor has misspoken or otherwise created an unnecessary or troublesome limitation in the claims, it is a self-inflicted wound. The public is entitled to rely on the words used provided the words used are interpreted fairly and knowledgeably. [Emphasis in the original.]
>
> [33] Claim construction requires that the disclosure and the claims be looked at as a whole "to ascertain the nature of the invention and methods of its performance, … being neither benevolent nor harsh, but rather seeking a construction which is reasonable and fair to both patentee and public" (*Consolboard* at p. 520; see also *Teva Canada Ltd. v. Pfizer Canada Inc.*, 2012 SCC 60, [2012] 3 S.C.R. 625 at para. 50). Consideration can thus be given to the patent specifications to understand what was meant by the words in the claims. One must be wary, however, not to use these so as "to enlarge or contract the scope of the claim as written and …

> understood" (*Whirlpool* at para. 52; see also *Free World Trust* at para. 32). The Supreme Court recently emphasized that the focus of the validity analysis will be on the claims; specifications will be relevant where there is ambiguity in the claims (*AstraZeneca Canada Inc. v. Apotex Inc.*, 2017 SCC 36, [2017] 1 S.C.R. 943 at para. 31; see also *Ciba* at paras. 74-75).
>
> [34]Finally, it is important to stress that claim construction must be the same for the purpose of validity and for the purpose of infringement (*Whirlpool* at para. 49(b)).

B. *Asserted Claims*

[89] Although Allergan asserted in its Further Amended Statement of Claim that Juno would infringe at least one of Claims 1, 5, 16, 19 and 20 of the 691 Patent, prior to trial Allergan informed the Defendant and the Court that it was only asserting infringement of two Claims:

(a) Claim 16: A composition comprising by weight 0.01% bimatoprost, 0.02% benzalkonium chloride, 0.268% sodium phosphate dibasic heptahydrate, 0.014% citric acid monohydrate, 0.81% sodium chloride, water, and wherein said composition is an aqueous liquid with a pH adjusted to 7.3.

(b) Claim 19: Use of a composition according to any one of claims 1 to 16 for treating glaucoma or intraocular hypertension in a mammal.

C. *Parties' Positions on Claims Construction*

[90] The parties both took the position that the claims mean what they say, and there is no particular question about the meaning of the key terms, as they would be understood by the POSITA.

[91] In regard to Claim 16, it is a formulation containing a well-known active ingredient, bimatoprost, as well as BAK, which is the most commonly-used preservative used in eye drops. The other excipients listed in Claim 16 are equally common, as is the adjustment of the pH of the composition to 7.3 (commonly done to correspond to the pH level of eye fluid).

[92] On Claim 19, the parties submitted that the use of the eye drop formulated in accordance with Claim 16 is quite straightforward and did not require any specialized knowledge.

D. *Analysis*

[93] The claims are quite straightforward, and a POSITA would understand them to mean what they say.

[94] Claim 16 is a composition claim, and all of the elements that are referred to are well-known and commonly used substances found in other eye drops. For the purposes of this case, the two key ingredients are 0.01% bimatoprost and 0.02% BAK by weight; a POSITA would interpret this as referring to 100 ppm bimatoprost and 200 ppm BAK.

[95] Similarly, a POSITA would understand that the adjustment of the aqueous liquid formulated with the ingredients listed in Claim 16 would have a pH adjusted to 7.3 so that it corresponded to the pH found in the human eye. Otherwise, the eye drop would irritate the eye.

[96] Claim 19 is a use claim, and a POSITA would interpret it as meaning what it says: using the eye drop formulated in accordance with claims 1 to 16 for treating glaucoma or intraocular

hypertension in a mammal. I will discuss below the pertinence of the reference in Claim 19 to the other claims listed in the 691 Patent, in particular Claim 1, but there is no question that the administration of an eye drop formulated in accordance with Claim 16 for treatment of these conditions would be a matter of routine for the Skilled Ophthalmologist.

[97] Nothing more needs to be said about claims construction in this case. The claims should be read in accordance with the plain meaning of their terms. As discussed below, the core of the dispute between the parties relates to the obviousness inquiry, in particular the nature of the inventive concept and whether the new formulation contained in Claim 16 was "obvious to try."

VII. Obviousness

A. *Legal Principles*

[98] The starting point on the law of obviousness is section 28.3 of the *Patent Act*, RSC 1985, c P-4 [*Patent Act*]:

Invention must not be obvious	**Objet non évident**
28.3 The subject-matter defined by a claim in an application for a patent in Canada must be subject-matter that would not have been obvious on the claim date to a person skilled in the art or science to which it pertains, having regard to	28.3 L'objet que définit la revendication d'une demande de brevet ne doit pas, à la date de la revendication, être évident pour une personne versée dans l'art ou la science dont relève l'objet, eu égard à toute communication :
(a) information disclosed before the one-year period immediately preceding the	a) qui a été faite, soit plus d'un an avant la date de dépôt de la demande, soit,

filing date or, if the claim date is before that period, before the claim date by the applicant, or by a person who obtained knowledge, directly or indirectly, from the applicant in such a manner that the information became available to the public in Canada or elsewhere; and	si la date de la revendication est antérieure au début de cet an, avant la date de la revendication, par le demandeur ou un tiers ayant obtenu de lui l'information à cet égard de façon directe ou autrement, de manière telle qu'elle est devenue accessible au public au Canada ou ailleurs;
(b) information disclosed before the claim date by a person not mentioned in paragraph (a) in such a manner that the information became available to the public in Canada or elsewhere.	b) qui a été faite par toute autre personne avant la date de la revendication de manière telle qu'elle est devenue accessible au public au Canada ou ailleurs.

[99] Justice Rothstein of the Supreme Court sets out the following four-part test in *Sanofi* at paragraph 67:

> In the result I would restate the *Windsurfing* questions thus:
>
> (1)(a) Identify the notional "person skilled in the art";
>
> (b) Identify the relevant common general knowledge of that person;
>
> (2) Identify the inventive concept of the claim in question or if that cannot readily be done, construe it;
>
> (3) Identify what, if any, differences exist between the matter cited as forming part of the "state of the art" and the inventive concept of the claim or the claim as construed;
>
> (4) Viewed without any knowledge of the alleged invention as claimed, do those differences constitute steps which would have

> been obvious to the person skilled in the art or do they require any degree of invention? [Emphasis added.]
>
> It will be at the fourth step of the *Windsurfing/Pozzoli* approach to obviousness that the issue of "obvious to try" will arise.

[100] In applying this test, the Court must be cautious not to employ hindsight bias in its obviousness analysis: *Canada LP/Valeant Canada SEC v Generic Partners Canada Inc*, 2019 FC 253 [*Valeant Canada*] at para 104; *Meda AB v Canada (Minister of Health)*, 2016 FC 1362 at para 138; *Bridgeview Manufacturing Inc v 931409 Alberta Ltd (Central Alberta Hay Centre)*, 2010 FCA 188 at para 50. On this point, I refer to the words of Justice James Hugessen in *Beloit Canada Ltd c Valmet Oy*, (1986) 8 CPR (3d) 289 at 295 (FCA):

> Every invention is obvious after it has been made, and to no one more so than an expert in the field. Where the expert has been hired for the purpose of testifying, his infallible hindsight is even more suspect. It is so easy, once the teaching of a patent is known, to say, "I could have done that"; before the assertion can be given any weight, one must have a satisfactory answer to the question, "Why didn't you?"

B. *Step 1 – The Skilled Person and their Common General Knowledge*

[101] As discussed above, there is no real debate about the notional POSITA. There was also broad agreement between the parties' experts on many aspects of the relevant CGK, but they disagreed on certain core elements. In addition, Juno's experts displayed some degree of confusion about what constitutes CGK as opposed to the "state of the art". I found that Juno's experts included many things in CGK that are more properly considered as part of the state of the relevant art.

(1) The POSITA

[102] As outlined in Part V above, “The Skilled Person”, there was no real dispute between the parties that the POSITA in regard to the 691 Patent consists of a team comprised of an ophthalmologist and a formulator. Both have some knowledge and experience relating to glaucoma and ocular hypertension. The Skilled Ophthalmologist has experience treating these conditions, and the Skilled Formulator has experience in the formulation of eye drops.

(2) The Common General Knowledge of the POSITA

(a) *Legal Principles*

[103] The CGK consists of what the POSITA would generally know and accept at the relevant time: *Sanofi* at para 37; *Mylan Pharmaceuticals ULC v Eli Lilly Canada Inc*, 2016 FCA 119 at para 24 [*Mylan*]; *Bell Helicopter Textron Canada Limitée v Eurocopter*, 2013 FCA 219 [*Eurocopter*] at para 64-65. CGK includes what the POSITA may reasonably be expected to know and to be able to find out; they are expected to be reasonably diligent in keeping up with advances in the field to which the patent relates: *Whirlpool* at para 74. It is not a memory test. The POSITA may be permitted to refer to standard texts and resources to “look things up”: *Novopharm Limited v Janssen-Ortho Inc and Daiichi Pharmaceuticals Co, Ltd*, 2007 FCA 27 at para 25(2).

[104] CGK does not include all the information in the public domain: *Eurocopter* at para 64. The Federal Court of Appeal recently confirmed this point in *Gemak Trust v Jempak Corporation*, 2022 FCA 141 at 95-96:

> A piece of particular knowledge as disclosed in a scientific paper does not become common general knowledge merely because it is widely read, and still less because it is widely circulated. Such a piece of knowledge only becomes general knowledge when it is generally known and accepted without question by the bulk of those who are engaged in the particular art": *Eli Lilly and Company v Apotex Inc,* 2009 FC 991 at para 97, quoting from *General Tire & Rubber Co v Firestone Tyre & Rubber Co Ltd,* [1972] RPC 457 at 482-483, itself quoting from *British Acoustic Films* (53 RPC 221 at 250).

[105] CGK must be distinguished from the "state of the art" which is a broader category encompassing all previously disclosed information in the field. The state of the art is the collection of learning in the field of the patent at issue and comprises all available teaching, however obscure or not generally accepted: *Mylan* at para 23. The state of the art is used to assess whether an invention was anticipated, or is obvious. CGK informs the way the claims and specifications are read by the POSITA: *Mylan* at para 25.

[106] Information only migrates from state of the art to CGK when a skilled person would become aware of it and accept it as "a good basis for further action": *Mylan* at para 24, quoting *General Tire & Rubber Co v Firestone Tyre & Rubber Co,* [1972] RPC 457 (CA) at 483.

(b) *Common General Knowledge of the POSITA*

[107] The POSITA in this case is a team comprised of a skilled ophthalmologist and formulator, and some parts of the CGK are common to both. It will be convenient, however, to discuss the CGK of the Skilled Ophthalmologist and then set out the CGK for the Skilled Formulator. The relevant date for assessing CGK is March 16, 2005 (the claim date).

(i) The CGK of the Skilled Ophthalmologist

[108] As of the relevant date, the CGK of the Skilled Ophthalmologist would include the following information, some of which is discussed above:

- The anatomy of the eye, including the protective corneal epithelial layer and its lipophilic quality, as well as the hydrophilic quality of the stroma;
- The causes of glaucoma and ocular hypertension, namely elevated IOP caused by an imbalance between the inflow and outflow of aqueous humour, which is associated with the degeneration of the trabecular mesh network;
- The risks associated with glaucoma and ocular hypertension, namely permanent vision loss due to damage to the ocular nerve caused by elevated IOP;
- The fact that to avoid vision loss, patients need to begin treatment to slow or halt the progression of these conditions before they become aware of any symptoms; and

- The importance of patient compliance, and the reasons some patients discontinue treatment or do not always follow their treatment regime (including disagreeable side-effects, the burden of taking several daily doses often involving a combination of drugs, and for some the physical difficulty of administering drops into their own eyes).

[109] The Skilled Ophthalmologist would also have known that the two basic treatment approaches for these conditions involved surgery or drug treatment, with the latter being the preferred option.

[110] In addition, the Skilled Ophthalmologist would have been aware of the categories of medication and the specific drugs that were commercially available at that time, as well as their main known benefits and side effects. These included:

- Beta-blockers such as timolol (marketed as TIMOPTIC®) and betaxolol (marketed as BETOPTIC®). These were effective at lowering IOP by reducing the inflow of aqueous humour, and they transformed glaucoma care when they were first introduced. They were a common, first line treatment option. However, experience showed that their effectiveness declined after several years, after which combination therapies using multiple medications had to be administered. In addition, they had systemic side effects that made them not suitable for persons with a variety of conditions, including certain cardiac diseases, asthma or severe chronic pulmonary obstruction. They can also cause sleep disorders, depression, headache, nausea and

dizziness, as well as ocular irritation and conjunctivitis. Some patients discontinued use because of these side effects;

- Prostaglandin Analogs ("PGA") such as latanoprost (marketed as XALATAN®) and travoprost (marketed as TRAVATAN®). These classes of drugs lowered IOP by increasing the outflow of aqueous humour. They became the preferred class of drugs for patients for whom beta-blockers were not suitable, and by March 2005 they were often the first line treatment because of their effectiveness in lowering IOP with relatively few side effects. A common side-effect was conjunctival hyperemia;

- Prostamides such as bimatoprost (which remains the only prostamide used in commercially available eye drops). Prostamides and PGAs are similar; they were described as "sibling drugs". Prostamides also reduce IOP by increasing the outflow of aqueous humour, and bimatoprost had the greatest average IOP reduction of all commercially available products. However, bimatoprost was also associated with the highest incidence of conjunctival hyperemia, and this became known to clinicians almost immediately after it entered the market. Bimatoprost had higher rates of hyperemia than PGAs. Clinicians found that 20-25% of their patients would discontinue use of bimatoprost because of the unwanted side effects.

[111] Reducing IOP was the only known treatment to prevent the progression of damage caused by glaucoma and IOH. It was known as of March 2005 that there are natural fluctuations in IOP, depending on an individual's age, heartrate and the time of day. Studies had shown that it was important to seek to maintain IOP within target ranges throughout the day and to avoid wide

fluctuations. For most patients with elevated IOP, the target was to reduce it to the “normal” range of around 21 mmHg (millimeters of mercury). However, studies had shown that for patients with advanced damage, it was necessary to seek to reduce IOP even lower, towards the 10-12 mmHg level.

[112] Finally, the Skilled Ophthalmologist would have known that as of 2005, eye drops were generally prescribed in multi-use bottles and therefore required a preservative to ensure that they remained safe for patients to use. BAK was (and remains) the most common preservative used in commercially available eye drops. BAK is a very effective preservative, but the Skilled Ophthalmologist would have known that it disrupted the surface of the eye.

[113] Despite the damage BAK caused to the eye, the Skilled Ophthalmologist knew that it was the most commonly used preservative, and was present in varying amounts in the different multi-use eye drops that were commercially available at that time. The Skilled Ophthalmologist wanted as many different treatment options as possible to deal with glaucoma, and had to accept the risk-benefit trade-offs associated with the different medications, including the presence of BAK.

[114] The Skilled Ophthalmologist knew that many patients required more than one drug to achieve an optimal IOP reduction towards the target level: approximately 30-40 % of patients are on more than one medication. This increased the difficulty of patient compliance and added to the cumulative risks associated with the presence of BAK in each medication that patients were required to take daily.

(ii) The CGK of the Skilled Formulator

[115] The CGK of the Skilled Formulator in March 2005 included the anatomy of the eye, the need to reduce IOP in the treatment of glaucoma and IOH, and the importance of patient compliance with the prescribed treatment regime as discussed above.

[116] Relating to the anatomy of the eye and the difficulty of formulating effective eye drops, the Skilled Formulator was aware of the ways in which the eye flushes foreign substances and the very limited amount of a drug that would actually penetrate the eye. At the relevant time, the CGK of the Skilled Formulator included various techniques to deal with this challenge, including ways of keeping the drug on the surface of the eye for a longer period (e.g. ointments or gels) as well as techniques to increase the rate of penetration so that more of the active ingredient reached the target location inside the eye (e.g. by using penetration enhancers).

[117] Associated with this, the Skilled Formulator's CGK included the routes of administration of ocular pharmaceutical formulations (eye drops), with the corneal pathway being the primary route. The Skilled Formulator was also aware of the two routes of absorption into the eye: transcellular (through the cell structure) and paracellular (using the gaps between cells). Related to this, the Skilled Formulator would have been aware of the barriers to penetration into the eye, including the lipophilic nature of the outer epithelial layer, which made it more difficult for water-based compounds to penetrate. A further barrier is the hydrophilic nature of the stroma, which is a layer deeper inside the eye. This meant that oily, lipid compounds could more easily penetrate the outer layer, but would then have greater difficulty getting through the stroma.

Water-based compounds faced the same barriers in reverse – being repelled by the outer layer, but easily penetrating the stroma.

[118] In addition, the Skilled Formulator would have been aware of the basic functions of different excipients in pharmaceutical formulations. For example, in addition to bimatoprost and BAK, Claim 16 of the 691 Patent lists a number of excipients and both expert formulators identified them as commonly-used and well-understood ingredients that served different functions in pharmaceutical formulations. A large part of the training of formulators involves studying these excipients so that they can choose the right combination to achieve the desired effects while avoiding or minimizing undesirable side effects.

[119] Claim 16 also refers to the composition being "an aqueous liquid with a pH adjusted to 7.3." The Skilled Formulator would have known that it was important to adjust the pH level of eye drops to match the level of the eye because a more acidic formulation would cause a stinging sensation.

C. *Step 2 – Inventive Concept*

[120] The second step of the *Sanofi* test is to "[i]dentify the inventive concept of the claim in question or if that cannot readily be done, construe it" (at para 67). This is a precursor to the third step, which involves identifying any differences between the state of the art and the inventive concept of the claim.

[121] This is a key dispute between the parties in this case. Allergan argues that the inventive concept of Claim 16 must be understood with reference to the specification in the 691 Patent, which makes clear that the inventive concept of the new formulation was to achieve IOP reduction that was comparable to that delivered by old LUMIGAN. Flowing from this, the inventive concept for Claim 19 was the use of the formulation set out in Claim 16 for the treatment of glaucoma or ocular hypertension.

[122] Juno disputes this, arguing that the inventive concept of Claim 16 is simply the formulation set out there; since the words are clear, Juno submits that there is no need to refer to the specification. Their argument also flows through to Claim 19, which they say simply involves using the formulation in Claim 16 to treat the listed conditions.

[123] In the analysis below, I will set out the opinions of the various experts as well as the submissions of the parties, followed by a discussion of the legal principles that govern this analysis and my conclusions on the question. One additional feature of this case is that the inventive concept of the 691 Patent has been determined in previous litigation conducted under the prior PM(NOC) regime. The relevance of those prior decisions is discussed below.

(1) The Experts' Opinions

[124] Allergan's experts advanced the view that Claim 16 is a formulation alone and that the language of the claim explained nothing about the utility of the formulation, why it is being claimed, what problem it purports to solve or what is inventive about it. Because of this, they assert that it is necessary to review the whole of the 691 Patent, not just the claims.

[125] Dr. Noecker set out his understanding of the inventive concept in Claim 16 in his expert report:

> 115. Read in the context of the patent as a whole, a Skilled Ophthalmologist would understand that the inventive concept of Claim 16 to be an ophthalmic formulation that achieves comparable IOP lowering efficacy to LUMIGAN® (0.03% bimatoprost) but contains less bimatoprost (i.e. 0.01%), achieved by increasing the concentration of BAK in the formulation (i.e. from 50 ppm to 200 ppm).

[126] In Dr. Noecker's opinion, the POSITA would arrive at this understanding based on the following elements of the 691 Patent:

- The Patent's title is "Enhanced Bimatoprost Ophthalmic Solution" – and since the POSITA would have been familiar with the existing commercial formulation for old LUMIGAN, as well as its shortcomings (in particular that it caused hyperemia), the POSITA would have understood that the new formulation was an "enhancement" over the existing product;

- The Examples in the Patent used old LUMIGAN as the "control" against which other formulations were compared;

- Example 2 demonstrated *ex vivo* that the aqueous humour concentration of bimatoprost increased by 57% with the addition of 200 ppm BAK, as compared to old LUMIGAN with 50ppm BAK;

- The results set out in Example 4 demonstrated that an ophthalmic solution containing 0.015% bimatoprost and 200 ppm BAK achieved significantly greater penetration of

bimatoprost across the epithelial layer than did old LUMIGAN, while a solution with a concentration of 0.01% bimatoprost and 200 ppm BAK would achieve IOP lowering efficacy comparable to old LUMIGAN. The results from this example would lead the Skilled Ophthalmologist to understand that a solution with less bimatoprost and more BAK than old LUMIGAN would achieve at least comparable efficacy;

- Example 5 stated that a formulation containing 0.015% bimatoprost and 125 ppm BAK achieved greater IOP reduction and less hyperemia than old LUMIGAN. From these results, the POSITA would expect that a formulation containing 0.01% bimatoprost and 200ppm BAK would provide comparable IOP lowering efficacy and less hyperemia than old LUMIGAN.

[127] Dr. Noecker's opinion is that the inventive concept for Claim 19 is the use of the formulation in Claim 16 to treat glaucoma and IOH.

[128] On both of these points, Dr. Berkland's expert report sets out similar conclusions. He asserted that the Skilled Formulator would recognize that the Claims in the 691 Patent have a lower concentration of bimatoprost and a higher concentration of BAK than old LUMIGAN, but they would not know from reading the claims why these changes had been made. Therefore, the Skilled Formulator would need to read the 691 Patent as a whole to understand why the new formulations were claimed and, more generally, to understand what is inventive about the claimed formulations. He also indicated that the inventive concept of Claim 19 is simply the use of the formulation set out in Claim 16 to treat glaucoma and IOH.

[129] In contrast, Juno's experts expressed the opinion that the inventive concept for the asserted claims is clear based on the wording of the claims themselves. They say the inventive concept of these claims generally correspond to the claim construction they advanced, which involved a straightforward reading of the terms of the two claims.

[130] Dr. Morgan stated that the overall inventive concept of the claims relates to the composition containing bimatoprost, BAK and other excipients as specified, where the compositions are in the form of aqueous liquid formulated for ophthalmic administration. Claim 16 also includes the pH of the composition as a component of the inventive concept. In his opinion, the inventive concept of Claim 16 is not limited to any particular use or level of performance, except that it is formulated for ophthalmic administration. Claim 19 is for the use of the formulation to treat glaucoma and IOH in a mammal.

[131] In support of his opinion about Claim 16, Dr. Morgan indicates that the wording of the claim is not ambiguous and the inventive concept is clear from its wording. He also points out that if the POSITA reviewed the disclosure of the 691 Patent to understand whether comparable effectiveness to old LUMIGAN was part of the inventive concept, they would not find any statements by the inventors to support a claim that the composition in Claim 16 achieves a comparable effect. There are no studies of clinical effectiveness, and no statement that the new formulation achieves a comparable effect. The patent does not disclose a problem associated with old LUMIGAN.

[132] Dr. Morgan acknowledged that Example 5 indicates that administration of a formulation (labelled formulation “J”) comprised of 0.015% bimatoprost, 125ppm BAK and 0.015% EDTA (ethylenediaminetetaacetic acid) resulted in greater IOP reduction and less hyperemia than old LUMIGAN. However, he pointed out that the inventors provided no information about how much of formulation J was to be applied, nor any test data to support this statement. He also notes that the other Examples provide evidence of the concentration of bimatoprost achieved by other formulations as compared with old LUMIGAN, but none of these provide any indication that the new formulations had a “comparable effect.” Because of the absence of statements about comparable effect or any data to support such a claim, Dr. Morgan states that even if the POSITA reviewed the entire 691 Patent, they would not understand a comparable effect to be part of the inventive concept.

[133] Dr. Alany’s opinion matches that of Dr. Morgan. He adds that while the POSITA would recognize that the formulation in the claims contains less bimatoprost than old LUMIGAN, and that the composition in Claim 16 is formulated for ophthalmic administration, they would also not find any statement that the formulation was just as effective (or more effective) as the commercially available old LUMIGAN product. He notes there are no statements in the claims regarding a reduction in hyperemia. Furthermore, the description in the 691 Patent does not contain any data or discussion regarding any technical advantages of the excipients in the formulations. Based on this, Dr. Alany’s opinion is that the inventive concepts of claims 16 and 19 are clear from the wording of the claims themselves. He states that even if the POSITA reviewed the description of the 691 Patent for help in understanding whether a comparable effect is part of the inventive concept, they would not see any assertion that the formulations of the

claims achieve a comparable effect, including clinical efficacy, to that delivered by old LUMIGAN.

(2) The Submissions of the Parties

[134] Allergan advances three main arguments on inventive concept.

[135] First, Allegan argues that there is no reason to depart from the inventive concept of the 691 Patent set out in prior decisions of this Court and the Federal Court of Appeal. In both *Apotex FC* and *Cobalt FC*, Justice O'Reilly of this Court found at paragraph 26 that "…reading the '691 patent as a whole, the inventive concept of Claims 16 and 19 is a formulation with a reduced [bimatoprost] but with comparable efficacy to old LUMIGAN, achieved by increasing BAK." This was specifically affirmed by the Federal Court of Appeal (*Apotex FCA*) at paragraph 7(i).

[136] Allergan argues that a finding on inventive concept is a question of law that is prima facie binding: *Bayer Inc v Apotex Inc*, 2016 FC 1013 [*Bayer*] at para 53; *Apotex Inc v Pfizer Canada Inc*, 2013 FC 493 at paras 11-12.

[137] Second, Allergan points out that the experts, including Dr. Alany, accepted that the patent was about an "enhanced" bimatoprost ophthalmic solution, and reading the patent as a whole makes it clear that the inventors were describing formulations that were just as or more effective than the commercially available old LUMIGAN. Allergan also notes that Dr. Morgan admitted that the data in Example 2 showed there is enhanced penetration of bimatoprost into the aqueous

humour, and that increasing the amount of BAK would increase the permeability of bimatoprost and thereby increase the efficacy of the lower dose.

[138] Allergan points to the consistent evidence of its experts that Claim 16 is merely a formulation (or recipe) and in order to understand its inventive concept it is necessary to examine the entirely of the 691 Patent. Allergan submits that this approach is consistent with the binding case-law, citing the recent decision of the Federal Court of Appeal in *Apotex Inc v Shire LLC*, 2021 FCA 52 [*Shire*]. Allergan argues that in *Shire*, the Court of Appeal rejected the argument that patent claims ought to be considered without regard to any features or advantages not specifically included in the claims, and noted that while identifying the inventive concept is informed by claim construction, it remains a distinct exercise. Based on this, Allergan asserts that its interpretation of the inventive concept of the claims – as a formulation with lower bimatoprost but comparable efficacy to old LUMIGAN, achieved by increasing BAK – should be adopted.

[139] In response, Juno asserts that the prior decisions are not binding nor persuasive, given that they were based on the former PM(NOC) regime. Juno submits that previous decisions under that regime had found that decisions made on applications to prohibit the issuance of an NOC were not binding in subsequent proceedings relating the validity of the same patent: *Bayer*; *Janssen Inc v Apotex Inc*, 2021 FC 7 [*Janssen FC* 2021] at paras 12 and 217; aff'd *Janssen Inc v Apotex Inc*, 2022 FCA 184 [*Janssen FCA*] at para 3.

[140] Juno submits that the identification of the inventive concept begins with the claims of the patent and only looks to the disclosure when necessary: *Eli Lilly Canada Inc v Mylan Pharmaceuticals ULC*, 2020 FC 816 at paras 291, 293, 297-298 and 301; *AstraZeneca Canada Inc v Apotex Inc*, 2014 FC 638 at paras 267-269. Any particular result from the alleged inventive concept that is said to be a basis for distinguishing over the prior art must constitute an essential element of the claim: *Hospira Healthcare Corporation v Kennedy Trust for Rheumatology Research*, 2020 FCA 30 at para 71.

[141] In this case, according to Juno, there is no reason to look at the disclosure in the patent because the inventive concept is clear from the terms of the claims themselves. The claims use well-known terms that can be understood without reference to the disclosure.

[142] Juno rejects the attempt by Allergan to import a requirement of comparable efficacy into the claims because it unnecessarily imports ambiguous aspects of the disclosure. It points out that Dr. Berkland's evidence was that a composition would be comparable if it fell within the error range of the control formulation in Example 4 of the 691 Patent, and that it would not mean "exactly the same" efficacy as old LUMIGAN but "should be about the same." Juno also notes that Dr. Berkland did not explain how he had followed his instructions to find a single inventive concept that flowed through the patent, but rather limited his evidence to only Claims 16 and 19.

[143] As for Dr. Noecker, Juno argues that despite testifying that the invention was clear, he could not explain how a formulation containing 0.005% bimatoprost and 100 ppm BAK (in accordance with the range set out in Claim 1) could provide comparable efficacy to old

LUMIGAN. In addition, Dr. Noecker could not identify a single inventive concept that flows through the entire patent.

[144] Instead, Juno argues that the inventive concept set out by Dr. Morgan and Dr. Alany should be preferred, noting their evidence that the wording of the claims was clear and there were no claims or evidence to support including comparable efficacy as part of the inventive concept.

(3) Analysis

[145] Dealing first with Allergan's argument regarding the prior decisions, I am not persuaded that I am bound by the prior determinations of the inventive concepts of Claims 16 and 19. In both *Apotex FC* and *Cobalt FC,* Justice O'Reilly stated at paragraph 26: "In my view, reading the '691 patent as a whole, the inventive concept of Claims 16 and 19 is a formulation with reduced [bimatoprost] but with comparable efficacy to old LUMIGAN, achieved by increasing BAK." This was specifically confirmed by the Federal Court of Appeal in *Apotex FCA* at paragraph 7(i). In the ordinary course of things, a ruling by the Federal Court of Appeal dealing with the same claims in the same patent would be binding on me.

[146] However, as counsel for Juno correctly points out, the prior determinations were made under the former PM(NOC) regime, which involved a different procedural framework and evidentiary process. Under the former regime, patent owners could bring an application to seek to prevent the Minister of Health from issuing an NOC, and these proceeded by way of affidavit evidence. In some cases, subsequent actions for patent infringement were launched, involving

the same parties and patent. That two-step system has been replaced by the current *PM(NOC) Regulations*, which provide for a single action, with all of the usual discovery rights and where *viva voce* evidence can be heard.

[147] Even under the old PM(NOC) regime, it was recognized that while claims construction and the determination of the inventive concept are questions of law, rulings on these questions made in the context of an application would only be *prima facie* binding on the judge hearing a subsequent patent infringement action. As Justice Simon Fothergill explained in *Bayer* at paragraph 53:

> To the extent that this Court may have discretion to follow or depart from the previous construction adopted in the NOC proceedings, I consider the Federal Court of Appeal's prior construction to be prima facie binding, but acknowledge that it may be revisited if warranted by the evidence. In other words, I will adhere to the construction given to the '426 patent by Justice Hughes and by the Federal Court of Appeal unless a party provides good reason not to. The same holds true when defining the "inventive concept" of the patent and determining the "promise" of the patent, both of which are aspects of claim construction and are therefore questions of law… [citations omitted]

[148] That approach applies with even greater force, it seems to me, now that the underlying legal framework has been changed. For example, Justice Michael Phelan issued one of the last decisions under the old PM(NOC) regime, followed by one of the first decisions under the new one, dealing with the same parties and same patent and claims: see *Janssen Inc v Apotex Inc*, 2019 FC 1355; and *Janssen FC 2021*. In the latter decision, Justice Phelan noted that the parties provided "new and better evidence… [and] [p]revious witnesses were open to examination on a more complete record resulting from the pre-trial discovery process." In addition, he "had the

advantage of hearing directly from witnesses… and [therefore] had better evidence, current legal teachings and more focused argument" (at para 10). Based on this, Justice Phelan concluded: "unless specifically adopted from the [earlier decision] the findings and comments in that decision are irrelevant to the trial [and] 'the Court is required to approach the case afresh with 'a mind willing to understand and be persuaded'" (at paras 11-12). In the result, Justice Phelan declared the patent invalid in the latter decision, reaching the opposite result to his earlier ruling.

[149] On appeal, the Federal Court of Appeal stated at paragraph 3: "…there is no dispute that, for the purposes of the Decision [under the new PM(NOC) regime] the Federal Court's prior findings were not binding on the parties or on the courts. The 2019 NOC proceeding involved a different evidentiary record, and the witnesses' testimony in that case was adduced by transcript rather than live in court" (*Janssen FCA*).

[150] I do not need to come to a final determination regarding the question of whether findings on matters of law (including claims construction and the inventive concept) are technically binding. At a minimum, it seems to me that the binding or persuasive force of the earlier decisions is significantly attenuated by the dramatic change in the legal framework.

[151] An additional factor that cements my determination on this point is that I do not have evidence about the factual record that was before the Court in *Apotex FC* or *Cobalt FC*. There is no dispute that the extent to which the earlier findings are *prima facie* binding on me depends in part on the factual record on which they were based. As confirmed by Justice Fothergill, the previous findings "may be revisited if warranted by the evidence" (*Bayer* at para 53). Allergan

acknowledged that the prior claims construction and determination of the inventive concept are both questions of law "with an asterisk" because they are sometimes embedded with factual determinations about what the POSITA would have thought or done.

[152] Absent evidence about the factual record on which the earlier rulings rest, I am not persuaded that I am bound to apply them. The change in the procedure under the new PM(NOC) regime that governed this proceeding reinforces this view. Like Justice Phelan in *Janssen* FC 2021, I have benefitted from hearing witnesses and the parties had the opportunity for greater discovery than was possible under the old regime. While I accept the importance of *stare decisis* and its cousin, judicial comity (see *Amgen Inc v Pfizer Canada ULC*, 2020 FC 522 at para 167), I am not persuaded that I am bound to follow the previous determinations of the inventive concept.

[153] Turning to the substance of the determination I am required to make on this point, I agree with Allergan that the recent Federal Court of Appeal decision in *Shire* is both binding and particularly pertinent to the case at bar. In that decision, Justice Donald Rennie set out several guiding principles, which help to orient the inquiry.

[154] First, "while the inventive concept is an attribute of the claims, it differs from claims construction… As such, though the process for the identification of an inventive concept bears a striking resemblance to that of claims construction… it is nonetheless a distinct, separate exercise" (*Shire* at para 68).

[155] Second, it is essential to recall that the inventive concept is part of the determination of obviousness, and "[its] purpose is to help determine what, if anything, makes the claim, as constructed, inventive… and the term 'inventive concept' is not materially different than the previously used term of 'solution taught by the patent…" (*Shire* at para 76, citations omitted).

[156] Third, if the inventive concept is not "readily apparent where there is agreement on it", it needs to be construed:

> To do that, the judge is first to determine whether it can be identified from the previously completed claims construction exercise. Second, where it is not possible to fully grasp the nature of the inventive concept solely from those claims, the judge may have regard to the patent specification to determine if it provides any insight or clarification into the inventive concept of the claim(s) in issue. If this step is necessary, "it is not permissible to read the specification in order to construe [the inventive concept of the] claims more narrowly or widely than the text will allow."
>
> (*Shire* at para 67, citations omitted.)

[157] Related to the third principle, Justice Rennie adopted the caution expressed in *Unilever PLC v Chefaro Proprietaries Ltd*, [1994] RPC 567 (Eng CA) at 580… that "[i]t is the 'inventive concept' of the claim in question which must be considered, not some generalized concept to be derived from the specification as a whole… [I]t is the inventive concept(s) of the claim(s) in issue that must the focus of the obviousness inquiry, not the inventive concept of the patent…" (*Shire* at para 69). Flowing from this, while a "single inventive concept must flow through a patent… each claim's specific inventive concept may be different" (*Shire* at para 77) and some repetition is permitted.

[158] Justice Rennie points out that the claims in issue in *Shire*, like the ones in *Sanofi*, are to bare chemical compounds and the "essential element of these claims is simply the chemical formula itself, which, standing alone, says nothing as to the 'inventiveness' of the patent claims. As such, it is necessary to turn to the specification for amplification" (*Shire* at para 72).

[159] In approaching this task, however, I underline the important caution that was endorsed by Justice Rennie in *Shire*, namely that it is the inventive concept of the claim in question that must be considered, not some "generalized concept to be derived from the specification as a whole" (*Shire* at para 69).

[160] Applying this guidance to the case before me, the first thing to note is that the parties do not agree on the inventive concept, and it is not "readily apparent" (*Shire* at para 67). Nor does it emerge from the claims construction set out earlier. While the parties were in agreement on the construction of the claims, they significantly diverge on the inventive concept.

[161] Although the claims in issue in this case are not identical to those in *Shire* (those claims are set out in Appendix "A" of that decision), I find that the same problem arises, because the recipe set out in Claim 16 and the use described in Claim 19 say nothing about the inventiveness of the claims.

[162] As noted previously, Claim 16 sets out the composition of an eye drop, listing the percentages by weight of each element that is included. The essential elements of that claim for the purposes of this case are the amount of bimatoprost and BAK included in the formulation.

Claim 19 is simply the use of that composition to treat glaucoma or IOH in a human: that is its essential element. These terms, standing alone, say nothing as to the inventiveness of the claims. Put another way, the wording of the claims do not, themselves, reveal the "solution taught by the patent." To do that, the construction of the inventive concept of the claims must be informed by the specification.

[163] I agree with Allergan that there are numerous decisions where this Court or the Federal Court of Appeal have turned to the specification to determine the inventive concept. In this regard, both *Allergan Inc v Canada (Health)*, 2011 FC 1316 [*Combigan*] and *Allergan Inc v Sandoz Canada Inc*, 2020 FC 1189 [*Rapaflo*] are instructive. In both of those cases, the claims bore a greater similarity to the ones in issue here as contrasted with the wording of the claims that were in issue in *Sanofi* and *Shire*, for example. It is significant that in both *Combigan* and *Rapaflo*, the inventive concept of the claims in issue was construed with reference to the specification because it was not possible to fully grasp the nature of the inventive concept solely from the wording of the claims in issue.

[164] The parties acknowledge that although the problem of hyperemia associated with old LUMIGAN was well known at the time Allergan developed the new formulation in Claim 16, a reduction in hyperemia forms no part of the inventive concept for either claim. Instead, the focus of the argument is whether the inventive concept of Claim 16 includes the idea that the new formulation would be just as or more effective than old LUMIGAN in lowering IOP, for the purposes of treating glaucoma or IOH in humans (Claim 19).

[165] I agree with Allergan that several elements of the specification support the view that the proper construction of the inventive concept animating Claim 16 includes the formulation is at least as effective as old LUMIGAN. The first indication of this is the title of the 691 Patent; "Enhanced Bimatoprost Ophthalmic Solution." Given that old LUMIGAN was the only bimatoprost product on the market at that time, the reference to "enhanced" invites a comparison to it, and indicates that the new formulation is better in some ways than the old one. This is reinforced by the Table at Figure 1 of the Patent, which sets out the aqueous humour concentration of old LUMIGAN, with 50 ppm BAK, while the next bar shows the higher concentration for a formulation with 200 ppm BAK.

[166] The fact that several Examples in the Patent show old LUMIGAN as the "control" in tests that examined the penetration of different formulations into the aqueous humour is a further indication that a comparison of the new formulation with the prior one is part of the inventive concept of Claim 16.

[167] Furthermore, the text that accompanies several of the examples makes clear that the inventors were comparing the different formulations with old LUMIGAN. In Example 2, Table 2 shows a higher concentration of bimatoprost with 200 ppm BAK as compared with a formulation that has 0.03% bimatoprost and 50 ppm BAK (the same concentrations as old LUMIGAN). The text in the description of Example 2 states:

> Test formulations containing 0.015%, 0.2%, 0.4% and 1.0% TPGS [a known penetration enhancer] resulted in a lower aqueous humour carbolic acid concentration comparted to Bimatoprost by 52%, 59%, 62% and 72% respectively. In contrast, 0.03% Bimatoprost containing 200 ppm BAK resulted in 57% higher

> aqueous humour AGN 191522 concentration compared to Bimatoprost (50 ppm BAK).
>
> While not intending to limit the scope of the invention in any way, or be bound by theory, compared to the Bimatoprost control, formulations containing TPGS resulted in decrease bimatoprost permeability. In contrast, formulations with higher BAK resulted in higher permeability.

[168] Example 3 sets out a variety of different formulations, once again showing 0.03% bimatoprost with 50 ppm BAK (which matches the components of the old LUMIGAN formulation) as the "Control". Most of the other formulations show less bimatoprost and more BAK, and some include another known penetration enhancer referred to as EDTA.

[169] Example 4 describes the process by which *ex vivo* tests were done using these formulations, with the results set out in Figure 2. Once again, a formulation with the same amount of bimatoprost and BAK as old LUMIGAN (described as the "Control") is the first result shown, together with the permeability results for the other formulations. The results show that formulations with 0.015% bimatoprost and 150ppm or 200ppm BAK (with our without the addition of EDTA) achieved significantly higher concentrations of bimatoprost in the aqueous humour than the Control. Once again, the results set out in Figure 2 invite a comparison of formulations using more BAK (with or without the addition of EDTA) with the permeability results for old LUMIGAN.

[170] Example 5 states that a drop of formulation J (which is described in Table 3 as comprising 0.015% bimatoprost, 125 ppm BAK and 0.015% EDTA) is administered once daily to the eye of a person suffering from glaucoma. It then states that after a few hours "intraocular

pressure drops more and less hyperemia is observed than would be observed for formulation A." As set out in Table 3, formulation A has the same amount of bimatoprost and BAK as old LUMIGAN.

[171] While none of the Examples use a formulation identical to that set out in Claim 16, they all show that formulations containing less bimatoprost and more BAK than old LUMIGAN had increased efficacy in penetrating into the aqueous humour.

[172] The consistency of these comparisons with old LUMIGAN combined with the idea expressed in the title that the new formulation is "enhanced" serves to confirm the construction of the inventive concept put forward by Allergan. It shows that what is "inventive" about the formulation in Claim 16 is that a formulation with less bimatoprost and more BAK will have efficacy that is equal to or greater than old LUMIGAN. Under Claim 19, efficacy refers to the treatment of glaucoma and IOH in humans, using the formulation created in accordance with the recipe set out in Claim 16.

[173] Dr. Morgan correctly observed that the only reference to IOP reduction in the 691 Patent is the statement in Example 5 that the administration of a drop of formula J once daily resulted in a drop in IOP and less hyperemia. He also properly observed that there are no test results to substantiate these statements. However, I am not persuaded that this undermines the construction of Claims 16 or 19 proposed by Allergan. Both expert ophthalmologists stated that the penetration of the active ingredient into the aqueous humour was the means by which IOP

reduction was accomplished (leaving aside surgery, which is not relevant here) and therefore the test results set out in the specification stand as a proxy for IOP reduction.

[174] Juno asserted that Allergan has failed to demonstrate that there is a single inventive concept that flows through the whole patent. In particular, Juno argues that there is no evidence from Allergan and no statement in the patent that would cover the full range of possible embodiments set out in the Claims. On this, Juno points out that Claim 1 refers to a composition comprising as little as 0.005% bimatoprost and 0.01% BAK, and there are no experimental results that show that such a formulation would have an equal or better efficacy than old LUMIGAN. Juno also submits that neither of Allergan's experts described such a single inventive concept; instead, they limited their evidence to Claims 16 and 19. Juno argues that Allergan's proposed inventive concept cannot stand because there is no evidence that it runs through all of the Claims.

[175] This argument cannot succeed, for several reasons. First, the description set out above shows a single inventive concept that flows through the patent: namely that formulations containing less bimatoprost and more BAK have equal or greater efficacy than the formulation containing the same amounts of these compounds as old LUMIGAN.

[176] Second, Claim 1 is not in issue – Allergan claims infringement only in relation to Claims 16 and 19. As Justice Rennie confirmed in *Shire*, it is the inventive concept of each claim that must be determined at this step, not the inventive concept of the patent as a whole. In this case only Claims 16 and 19 are asserted by Allergan, and that is the focus of the analysis.

[177] It is true that Claim 19 refers to other formulations set out in other Claims that are not asserted by Allergan in this case. That fact cannot, in my view, affect the construction of the inventive concept vis-à-vis the specific claims in issue here. In this regard, it is important that the legal effect of the judgment and Order in this case is limited. I find that Claim 16 is valid, and Claim 19 is valid insofar as it is dependent on Claim 16. I need not, and do not, pronounce on any other aspect or dimension of Claim 19.

[178] The inventive concept of Claim 19 in relation to other claims, not asserted by Allergan here, is best left for another day.

[179] Juno's argument that Allergan's definition of the inventive concept imports a generalized concept from the specification also cannot succeed. While it is true that Allergan's witnesses did not offer a precise definition of the term "comparable" efficacy, I find that is not determinative. The idea that the formulation in Claim 16 will provide equal or greater penetration of bimatoprost into the aqueous humour, thereby reducing IOP in the treatment of glaucoma or IOH under Claim 19, is amply substantiated by the specification in the Patent, as discussed above. Allergan's patent does not rest on any claim of mathematical precision in this regard. On this point, I find Dr. Berkland's evidence that "comparable" would mean delivering a similar amount of bimatoprost into the eye to be apt.

[180] Rather than importing a generalized concept from the specification, the interpretation of the inventive concept I adopt here is based on a reading of the claims informed by the specification.

[181] For all of the reasons set out above, I am persuaded that the inventive concept of Claim 16 is a formulation with less bimatoprost but with comparable efficacy to old LUMIGAN, which is achieved by including more BAK than is found in old LUMIGAN. The inventive concept of Claim 19 is the use of this formulation for the treatment of glaucoma and IOH in humans.

D. *Step 3 – Differences between the State of the Art and the Inventive Concept*

[182] The third step of the *Sanofi* test requires the Court to "[i]dentify what, if any, differences exist between the matter cited as forming part of the 'state of the art' and the inventive concept of the claim or the claim as construed." On this, it is important to recall that the state of the art, or prior art, is much wider than the CGK; it includes any of the relevant literature that was available as of the relevant date (*SNF Inc v Ciba Specialty Chemicals Water Treatments Ltd*, 2017 FCA 225 at para 50).

[183] The third step of the *Sanofi* test sets the stage for the fourth and final step, which focuses on whether bridging the gap identified by the differences required any degree of inventiveness. The parties focused on much of the same prior art, but differed as to the proper understanding of what that literature teaches as it applies to the case.

[184] As noted in the last section, the inventive concept of the 691 Patent involves three key elements (all in relation to old LUMIGAN): (1) reducing the amount of bimatoprost; (2) increasing the amount of BAK; (3) doing 1 and 2 in order to achieve equal or greater IOP reduction. These three elements provide a useful way of addressing the debate concerning the prior art.

(1) Reducing the Amount of Bimatoprost

[185] Allergan submits that the prior art showed that reducing the amount of bimatoprost (the active ingredient) in the formulation would be expected to decrease its efficacy in reducing IOP. Old LUMIGAN, with 0.03% bimatoprost, was very effective in reducing IOP; indeed, it had the greatest IOP reduction of any commercially-available product in 2005. Reducing that concentration by two-thirds to 0.01 % was expected to have a negative impact on the overall efficacy of the product.

[186] The key piece of prior art on this point is the Laibovitz article: Robert A. Laibovitz et al, "Comparison of the Ocular Hypotensive Lipid AGN 192024 with Timolol" (2001), Vol 119 Arch Opthamolo 119:994-1000 [Laibovitz]. This article reported on the results of a 30-day, randomized, investigator-masked clinical trial involving 100 patients with elevated IOP. Non-preserved formulations (i.e. containing no BAK) of 0.003%, 0.001% and 0.03% bimatoprost were administered once daily for 3 weeks and then twice daily for 1 week. The control vehicle was 0.5% timolol administered twice daily for 4 weeks.

[187] Laibovitz reports that all of the formulations of bimatoprost used in the trial were "safe, well tolerated and effective" and that they "provided superior ocular hypotensive efficacy and better diurnal IOP control than timolol." More specifically, Laibovitz reports that the 0.01% formulation achieved a 20.7% reduction in IOP (measured as mean change from baseline) whereas the 0.03% formulation resulted in a 29.6% reduction. In the article, these results were

contrasted with the 12.9% reduction achieved by timolol. Laibovitz concluded that the 0.03% formulation had the best therapeutic profile of the three bimatoprost formulations tested.

[188] For the purposes of this analysis, it is the comparison between the two bimatoprost formulations that is particularly relevant. Allergan asserts that Laibovitz shows that a reduction in the percentage of bimatoprost in the formulation would be expected to cause a decrease in its efficacy in achieving IOP reduction.

[189] Dr. Noecker's evidence is that the difference in IOP reduction between the 0.01% and 0.03% bimatoprost formulations was important because it represented a significant reduction in efficacy. According to Dr. Noecker, a skilled ophthalmologist in 2005 would have been looking for a product that reduced IOP by at least 30%, because that result was already achievable using XALATAN (latanoprost) and old LUMIGAN delivered similar results. He testified that Laibovitz used timolol because it was a long-standing product that was treated as a benchmark by the U.S. Food and Drug Administration (FDA) in assessing new drugs to treat glaucoma and IOH. According to Dr. Noecker, however, the IOP reduction comparison with timolol was not particularly significant, because newer drugs produced better results.

[190] In contrast, Dr. Morgan testified that a reduction in IOP of 20% was clinically significant, and therefore the results for the 0.01% bimatoprost formulation would have been of interest to the Skilled Ophthalmologist. Dr. Morgan testified that different patients needed different treatments, and so he disagreed with Dr. Noecker's target of at least 30% IOP reduction. He agreed with Dr. Noecker that for patients with significant damage due to glaucoma or with very

high IOP, the target would be to reduce their IOP as much as possible to the low teens. However, Dr. Morgan's evidence is that for other patients, a more modest reduction in IOP such as the 20% provided by the 0.01% formulation would be clinically acceptable.

[191] Dr. Morgan described timolol as the "gold standard" against which new glaucoma medications were compared, but he agreed with Dr. Noecker that by 2005, it was known that prostaglandin medications provided better IOP reduction than timolol. Allergan submits that it is significant that Dr. Morgan acknowledged in cross-examination that the IOP lowering efficacy of 0.01% bimatoprost was worse than for other prostaglandin eye drops commercially available in 2005.

[192] The expert formulators also addressed Laibovitz. Dr. Berkland testified that a Skilled Formulator would have been interested in the different formulations and their results, but would have deferred to the Skilled Ophthalmologist's assessment of the clinical effectiveness of the different results. For Dr. Berkland, the key take-away from Laibovitz is that it confirmed what his intuition would have told him – namely, that reducing the concentration of bimatoprost in a formulation would decrease its efficacy in lowering IOP.

[193] Dr. Alany's evidence on Laibovitz went well beyond that of Dr. Berkland. He testified that a Skilled Formulator would have concluded based on the test results that the 0.01% bimatoprost formulation provided clinically effective results. He also expressed views on the motivation to reduce the amount of bimatoprost in the formulation to deal with the hyperemia

problem associated with old LUMIGAN, as well as on the reason to decrease bimatoprost while also increasing the concentration of BAK. These points are discussed below.

[194] I find that Dr. Alany's opinions on the efficacy of the 0.01% formulation went beyond the expertise of the Skilled Formulator. Dr. Berkland and Dr. Alany agreed that the results from Laibovitz would have been instructive to a formulator to the extent the data confirmed that lowering the concentration of bimatoprost resulted in less IOP reduction, but beyond that I do not put any weight on Dr. Alany's opinion about the potential effectiveness of the 0.01% formulation.

[195] Based on a careful examination of the experts' evidence, in my view some of the areas of purported disagreement between them are of no importance to this case. For example, there was a minor skirmish concerning Dr. Morgan's description of timolol as the "gold standard" of glaucoma treatments in 2005, but in the end he agreed with Dr. Noecker that it was simply a common benchmark standard used by regulators to compare newer treatments. Dr. Morgan's evidence was that by 2005, the prostaglandin class of drugs were the first line treatment options.

[196] Similarly, while the experts expressed different views regarding the target or goal for IOP reduction for a new medication, I find that this apparent disagreement is of no consequence. Dr. Noecker testified that the target should be at least 30%, because that level of reduction was possible using XALATAN (latanoprost). In contrast, Dr. Morgan stated that a reduction of 20% would be clinically effective.

[197] Both expert ophthalmologists agreed that given the wide array of different patient needs, the Skilled Ophthalmologist was looking for any and all drugs that could provide more options to treat the condition. Their evidence aligned on the key point that they welcomed new developments in the field because sometimes a patient's individual circumstances prevented the use of the usual "first line" treatment, and a significant percentage of patients required a combination of daily medications to reach their target IOP reductions. In the real world, ophthalmologists were open to any solution that worked, and accepted that different medications had different risk-benefit profiles.

[198] Dr. Noecker testified that his most important job was to prevent patients from going blind by lowering their IOP, and any drug that could contribute to that goal would be clinically useful. However, I also put considerable weight on Dr. Noecker's evidence that in treating glaucoma, the Skilled Ophthalmologist "always wants to get [their] best shot in", and only moved to alternative or combination therapies if that first-line treatment does not prove to be effective or was contra-indicated because of a particular patient's condition. On that score, both experts agreed that by 2005, the PGA class of medication had succeeded in reducing IOP by up to 30%, and so any new medication had to provide equal or better efficacy to be clinically useful.

[199] I should note here that Juno correctly pointed out that in one part of his expert report, Dr. Noecker mistakenly referred to the Laibovitz formulations as "preserved" (i.e. including BAK or an equivalent preservative). The article clearly states that the study was based on non-preserved formulations. However, I reject Juno's assertion that this mistake significantly diminishes Dr. Noecker's credibility. I say this for three reasons. First, Dr. Noecker readily acknowledged the

error when it was pointed out to him in cross-examination. He stated: “I misspoke”. Second, Dr. Noecker is obviously familiar with the Laibovitz article; he testified that he had read it “hundreds of times probably.” Related to this, Dr. Noecker correctly referred to it using non-preserved formulations at paragraph 196 of his Expert Report. Finally, it is not evident that Dr. Noecker’s evidence on the IOP reduction of the two bimatoprost formulations was dependent upon or affected by the question of whether they were preserved or not. For all of these reasons, while I acknowledge Dr. Noecker’s mistake on this point, I am not persuaded it should diminish the credibility of his evidence.

[200] Juno also submitted that Dr. Noecker’s evidence on Laibovitz was flawed because he reported that “reducing the concentration of bimatoprost from 0.03% to 0.01% directly correlated with a loss in efficacy”. However, Juno argues that Dr. Noecker was forced to acknowledge in cross-examination that there was not a direct, linear reduction, because a two-thirds reduction in the concentration of bimatoprost resulted in only a one-third reduction in IOP-lowering efficacy. I am not persuaded that this is of any significance, because Dr. Noecker’s report did not claim a linear relationship. Rather, his evidence accurately described the results reported in Laibovitz that a reduction in the percentage of bimatoprost in the formulation was directly correlated with a lowering of the IOP reduction. He did not assert that there was a linear relationship.

[201] In the end, I find there is no real dispute about the results of the Laibovitz study relating to the reduction of IOP (I note here that Dr. Morgan expressed some doubts regarding the reported incidence of hyperemia, which is discussed below). While Dr. Morgan stated that the IOP reduction for the 0.01% bimatoprost formulation was a “therapeutically satisfactory result”

that was “clinically acceptable”, he also acknowledged that it was worse than for the PGA class of drugs that was commercially available in 2005. His evidence on this point matches that of Dr. Noecker.

[202] I prefer Dr. Noecker’s testimony on this point. Dr. Morgan emphasized that both bimatoprost formulations were at least as good as timolol in reducing IOP, and he described timolol as the “gold standard” in glaucoma treatment as of 2005. However, in cross-examination Dr. Morgan acknowledged that by 2005 the PGA class of medications had eclipsed timolol; his evidence was that they had “transformed glaucoma care”. He also admitted that in order for a PGA medication to be of interest as of 2005, it had to offer some significant benefit over latanoprost, which by then had become the first line treatment because of its success in lowering IOP and its relatively low incidence of side effects.

[203] For all of these reasons, I am persuaded by Allergan’s argument that in 2005, the state of the art taught that reducing the concentration of bimatoprost in a formulation was likely to reduce its efficacy in lowering IOP. This is significant because lowering IOP is the most important goal of treatment for glaucoma and IOH, and as of 2005, LUMIGAN RC and the PGA class of medications had set a benchmark of IOP reduction in the mid-20% to 30% range.

[204] This is the first important difference between the prior art and the inventive concept of Claims 16 and 19.

(2) Increasing the Amount of BAK

[205] Allergan argues that the prior art teaches away from increasing the amount of BAK in the formulation, because it was known to be cytotoxic and there was a trend away from using BAK in ophthalmic medications. In 2005, most ophthalmic medications were delivered using multi-use containers that could be sources of bacteria. Because an infection in the eye can have dire consequences, regulators required a preservative to be included in these formulations. The trend away from BAK asserted by Allergan involved replacing it with another preservative, reducing its concentration, or moving to single-use eye drop containers.

[206] Allergan points out that 50 ppm BAK had been found to be effective as a preservative in old LUMIGAN, and there was no reason to consider increasing it. If anything, the state of the art consistently recommended keeping the concentration of BAK as low as possible.

[207] Allergan contrasts the evidence of its experts as against those relied on by Juno. Allergan argues that while its experts accurately described both the risks and benefits associated with BAK, the experts for Juno minimized or ignored these risks.

[208] Juno submits that Allergan's evidence is unduly tilted towards emphasizing the risks associated with using BAK in ophthalmic formulations. It points out that as of 2005, BAK was the most commonly used preservative found in a wide array of eye drops, and this continues to be the case today. Juno asserts that as of 2005, there was not a major trend away from preserved formulations towards preservative free eye drops. Indeed, at that time one of the most popular

and effective glaucoma medications was XALATAN (latanoprost), containing 200 ppm BAK. Based on the common use of BAK as a preservative in eye drops, Juno asserts that there was no gap between the state of the art and inventive concept insofar as it relates to increasing the amount of BAK to match the concentration in the most widely prescribed glaucoma medication then on the market.

[209] With this background, I turn to a review of the experts' evidence.

[210] Dr. Noecker's evidence is that the prior art taught away from increasing BAK because it is cytotoxic. He relies on a number of publications, but a key reference is an article by Pisella et al, which reported on a study of 4,107 patients, of whom 85% used preserved eye drops and 13% received preservative free eye drops: P J Pisella et al, "Prevalence of ocular symptoms and signs with preserved and preservative free glaucoma medication" (2002) 86 Br J Ophthalmol 418 [Pisella]. Pisella reports that the "use of preserved eye drops greatly increases the frequency of ocular irritation in glaucoma patients. Moreover, the frequency of signs and symptoms is correlated with the number of preserved eye drops used" (at 422).

[211] Pisella also states that "a change from a preserved to preservative free glaucoma eye drop, or even a reduction in the number of preserved eye drops used is associated with a significant decrease in the frequency of signs and symptoms of ocular irritation. This also shows that preservative adverse reactions are reversible and that removing preservatives is of benefit to glaucoma patients…" (at page 422). In addition, Pisella indicates "…the toxicity of preserved

eye drops is strongly suspected to impair the efficacy of subsequent surgery for the glaucoma, which constitutes a real healthcare concern."

[212] Dr. Noecker noted that the Skilled Ophthalmologist would have agreed with the conclusion of Pisella at page 422:

> The exclusive use of preservative free eye drops or even a reduction of the number of preserved eye drops used clearly reduces the signs of ocular surface irritation in glaucoma patients. Overall, preservative free eye drop products have a significant medical advantage.

[213] In addition, Dr. Noecker relied on an article he co-authored with Lisa Herrygers and Raana Anwaruddin titled "Corneal and Conjunctival Changes Caused by Commonly Used Glaucoma Medications" (2004), Vol 23 Cornea 490, which reports on experiments done using commonly prescribed glaucoma medications preserved with various concentrations of BAK, as well as drops using another preservative called Purite. The experiments showed that glaucoma medications containing higher levels of BAK resulted in greater corneal damage than medications preserved with Purite or with lower levels of BAK. On this latter point, the article notes that LUMIGAN RC had the lowest concentration of BAK of any of the glaucoma medications in the study, and that it produced correspondingly lower incidence of damage to the cornea.

[214] Dr. Noecker also cited a number of other articles that reported on the negative effects of using BAK, all of which supported his evidence that as of 2005, there was a trend away from

using BAK, either replacing it with another preservative or moving to a preservative free solution.

[215] Dr. Morgan had less clinical familiarity with non-preserved eye drops, since he testified that he did not use them at that time. He testified that preservative-free preparations were not generally available as of 2005, and so he did not address that in his expert report.

[216] Dr. Morgan disagreed with Dr. Noecker's opinion that the state of the art in 2005 taught away from using BAK. In his expert report, Dr. Morgan mentions that it was known that BAK could irritate the corneal surface and that some patients might develop a sensitivity or intolerance to it with chronic use. Despite this, Dr. Morgan's opinion is that the Skilled Ophthalmologist would have known that BAK was generally well tolerated and suitable for widespread clinical use.

[217] In addition, Dr. Morgan's Report included the following statement:

> To my recollection, in ophthalmology there was some general discussion regarding a move away from BAK after 2005 to reduce side effects, but that was driven by commercial pressure from some pharmaceutical companies taking the view that non-BAK eye drops were better. However, this discussion did not generate much commentary by ophthalmologists at the time of March 2005.

[218] In Dr. Morgan's view, Dr. Noecker placed too much emphasis on the negative aspects of BAK. According to Dr. Morgan, a more balanced view was presented in an article by Mark B Ableson and Kate Fink, "How to Handle BAK Talk" (2002), Review of Ophthalmology 52 [Ableson].

[219] Dr. Morgan stated that Abelson discussed the pros and cons of using BAK. The authors point out that some of the reported harms caused by BAK are based on an unrealistic dosage regime that does not replicate the way eye drops work in humans, both in respect of the amount of BAK to which the eye is exposed and the length of time BAK is present on the surface of the eye. Dr. Morgan cites the conclusion from Abelson that despite the fact that there are complications associated with its use, one can measure support for it by looking at "the list of eye drops that contain it and the millions of patient-years for which these drops have been safely used" (Abelson at 54).

[220] In response, Dr. Noecker stated that while Abelson criticizes the many studies that examined the use of BAK in animal models, he did not address other evidence about BAK's harms that were based on large-scale human studies, including Pisella. In Dr. Noecker's view, Dr. Morgan presented an overly positive assessment of the Abelson article, and he stood by his opinion that as of 2005 there was a trend away from using BAK for treating chronic conditions like glaucoma.

[221] The evidence of the expert formulators was generally consistent with the evidence of the respective expert ophthalmologists. Dr. Berkland testified that it was well known in the art that increasing BAK increased the damage to the corneal cells, and that increasing the amount of BAK in a formulation increased the risk of damaging the epithelium. He agreed with Dr. Noecker's opinion that as of 2005, the research supported moving away from BAK, and this was evident because commercially available glaucoma medications were doing exactly that.

[222] Dr. Berkland disagreed with the view expressed by Juno's experts that as of 2005 it would not have been unusual to use up to 200 ppm BAK because it was already approved at that level for XALATAN (latanoprost). In Dr. Berkland's view, the Skilled Formulator would have understood that the state of the art explained that such a high level of BAK was used because it was needed in order to get the latanoprost into solution. On this point, Dr. Berkland pointed to the teaching from the Asada Patent (CA 2,498,233), which revealed that it was necessary to use at least 100-150 ppm BAK to keep latanoprost in solution. Otherwise it did not dissolve completely, referred to as the "white turbidity" problem. There is a preference for eye drops to be clear solutions, for obvious reasons. Asada studied the possibility of lowering the concentration of BAK below the 200 ppm that had been used in XALATAN.

[223] According to Dr. Berkland, the Skilled Formulator would have known in 2005 that the 200 ppm BAK in the formulation for XALATAN was complexing with the latanoprost, and so the full amount was not free in the solution. His evidence was that this attenuated the harmful effect of BAK on the cornea, because some of the 200 ppm was complexed with the latanoprost, and so it was "not roaming around [in the eye]…"

[224] For his part, Dr. Alany's evidence about BAK focused largely on its utility as a penetration enhancer, which is discussed in the next section. Regarding its use as of 2005, Dr. Alany's evidence was that the Skilled Formulator would know that BAK was commonly used in commercial ophthalmic products in a range of concentrations from 40 ppm to 200 ppm, with 100 ppm being the most common. He also indicates that the Skilled Formulator would have believed

that it was safe to use a concentration of up to 200 ppm because XALATAN (latanoprost) had already been approved at that level.

[225] Dr. Alany's opinion is that the Skilled Formulator would balance the toxicity concerns associated with BAK against the advantages of avoiding infection and increasing the penetration of bimatoprost, all with a view to the ultimate goal of preventing subsequent loss of vision. Furthermore, any damage to the corneal epithelium due to BAK would be reversible, even with chronic use, because epithelial cells replenished every three days.

[226] I begin my analysis by noting that there is support in the literature for the positions of both sides on this point. Allergan is correct that as of 2005, the state of the art contained multiple expressions of caution against using BAK or at the very least, minimizing the amount used, because of concerns about its impact on the corneal epithelial cells. This was a particular concern where the eye drops were used to treat chronic conditions such as glaucoma, because of the cumulative effect of daily administration and the stacking effect of daily use of multiple eye drops containing BAK.

[227] On the other hand, Juno correctly points out that despite these concerns, BAK was the most commonly used preservative as of 2005 (and remains so today). Both expert ophthalmologists explained that in the real world, they had to accept that multi-use containers were in widespread use for ophthalmic medications, and therefore a preservative was required. Juno points to an article by Dr. Noecker and Dr. Eve Higginbotham, "Point Counterpoint: Does Glaucoma Medications' BAK Content Make a Difference in Clinical Practice" (May-June 2007)

Glaucoma Today. In this piece, which is not part of the relevant "state of the art" because it was published after March 2005, Dr. Noecker expressed concerns about the damage caused by BAK and its potential to compromise the future success of other medical or surgical interventions. On the other hand, Dr. Higginbotham pointed out that the presence of BAK is not particularly relevant in clinical practice, given the different classes of treatment and methods available to increase the success of future procedures despite any damage caused by BAK. Dr. Higginbotham noted that preservative-free timolol has not penetrated the clinical practice, and she predicted a similar fate for other non-preserved formulations.

[228] This is consistent with the evidence of Dr. Noecker. As he stated, in the real world clinical ophthalmologists have to "pick [their] poison" and in 2005, he regularly prescribed effective glaucoma medications that contained BAK despite the dangers associated with its use.

[229] The question for analysis here, however, is whether there was a gap between the state of the art and the inventive concept, more specifically the component of the inventive concept that involved increasing the amount of BAK in the formulation of old LUMIGAN. On this, I find that Juno's position is not supported by a balanced assessment of the state of the art.

[230] I am not persuaded by Juno's argument that the use of BAK in concentrations ranging from 100-200 ppm in other medications indicated that there was not a trend towards minimizing or eliminating it from ophthalmic formulations as of 2005, or that this fact outweighed the concerns about BAK's harmful effects that are expressed in the state of the art.

[231] First, I accept Dr. Berkland's evidence regarding the 200 ppm BAK in XALATAN (latanoprost). The Asada patent shows that at least 100 ppm BAK was needed to get latanoprost into solution, which is a necessary step in formulating an effective eye drop. There is no evidence to contradict Dr. Berkland's opinion that some portion of the 200 ppm BAK in XALATAN was complexing with latanoprost, and so it was not available to harm the corneal surface.

[232] Second, I accept Allergan's submission that Dr. Morgan's lack of experience with non-preserved eye drops may reflect the practice in Britain (where his clinical practice is located) but does not represent the state of the art in Canada or the United States as of 2005. There are also publications that discuss the use of preservative-free glaucoma medications in France during the relevant period. The record shows that at that time several ophthalmic medications were being re-formulated to replace BAK with another preservative or to create preservative-free alternatives. This supports Allergan's position that as of 2005 there was a trend away from using BAK.

[233] Furthermore, I find that Dr. Morgan's credibility on the relative balance of risk and benefit associated with BAK is diminished because he failed to mention significant studies showing risks associated with it. In particular, I note that in cross-examination, Dr. Morgan stated that he had read the Pisella article, and acknowledged that the article expressed a concern about the harmful effects associated with the long-term use of BAK. However, he did not mention it in his expert report, nor did he refer to other articles in the state of the art based on

human studies that showed the harmful effect of BAK and recommended that it be minimized or eliminated.

[234] In addition, I find Dr. Morgan's credibility on this point is reduced by the cumulative impact of three other things. First, he relied on the European Glaucoma Society Guidelines [EGS Guidelines] published in 2003 for a number of points in his evidence regarding the use of BAK in commercially-available products, but in cross-examination he acknowledged that he did not mention the following caution set out on the first page of that document:

> It is important when selecting medical treatment of glaucoma to understand not only the aims of therapy, but also the mode of action, side effects and contraindications of each individual medication.
>
> It is worth remembering that the preservatives contained within topical eye drop preparations may cause inflammatory conjunctival side effects and cytotoxic effects on the ocular surface. It is therefore important to consider the use of preservative-free preparations/delivery systems.

[235] It is troubling that Dr. Morgan did not include any mention of this in his reports or testimony until it was drawn to his attention in cross-examination. A balanced and objective presentation should have included some mention of it.

[236] In a similar vein, Dr. Morgan's report stated that there was some discussion about a move away from BAK after 2005, which he attributed to pressure from some pharmaceutical companies. He did not refer to any similar discussion prior to 2005. In cross-examination, Dr. Morgan acknowledged that based on the EGS Guidelines, and papers by Pisella and Baudouin, there was discussion about moving away from BAK prior to 2005. He testified:

> Yes. Having discussion after 2005 does not preclude discussion prior to 2005. I was just asked was there discussion after 2005…. I didn't say there was no discussion before 2005. I just said there was discussion after 2005. I wasn't asked that question, so I didn't address it.

[237] Dr. Morgan's knew that the relevant date for this patent was March 16, 2005, based on his instructions from legal counsel, and he knew that the state of the art prior to that date would be important. He knew that there are two key differences between the old LUMIGAN formulation and new LUMIGAN RC: reducing the amount of bimatoprost and increasing the amount of BAK. He knew that Dr. Noecker's report stated that there was a trend away from BAK as of 2005. Despite this, Dr. Morgan did not mention any discussion of moving away from BAK prior to 2005, although he acknowledged that such discussions had occurred.

[238] Finally, although Dr. Morgan's expert report did not include any mention of the concerns about BAK's toxicity expressed in the state of the art, he acknowledged in cross-examination that the Skilled Ophthalmologist would have considered safety and toxicity concerns as being part of the state of the art.

[239] For all of these reasons, I find Dr. Morgan's evidence about the state of the art regarding BAK to be less than persuasive.

[240] I find Dr. Noecker's evidence on this point to be more reliable. He supported his opinion with reference to the ample evidence in the state of the art showing that as of 2005 there were concerns about using BAK in eye drops, especially for chronic conditions or where multiple medications containing BAK were used. However, Dr. Noecker also acknowledged that he

prescribed glaucoma medications containing BAK as of 2005, because he had to "pick his poison" and these formulations were the most effective way of treating the condition and preventing patients from going blind.

[241] In summary on this point, I find there was a significant difference between the state of the art as of March 2005 and the inventive concept of a significant increase in the amount of BAK in the formulation. The following summarizes the key findings of a selection of the relevant state of the art:

- BAK is cytotoxic, and causes significant corneal and conjunctival irritation and epithelial erosion (Easty and Sparrow, *Oxford Textbook on Ophthalmology*, (1999) vol 1, at p.59);

- BAK is "one of the most disruptive ophthalmic additives to the stability of the lipid film and to corneal epithelial membranes" (Sean C Sweetman, ed, *Martindale: The Complete Drug Reference*, 2002, 33rd edition, at p.1133);

- Although most side-effects associated with BAK are reversible, some effects can be irreversible (Peter A. Netland and Robert C. Allen, *Glaucoma Medical Therapy*, at p.10);

- The effects of BAK on human corneas have been confirmed in large-scale human studies, not only in experiments using rabbit or other animal eyes:

    - Pisella;

- Cecile Beden et al, “A Comparative Study of the Ocular Tolerance After Administration of Anti-Allergic Eye Drops With or Without a Preservative (2004) Therapie Mar-Avr 59(2):259-64;

- The concerns about the use of BAK increased where multiple BAK-preserved medication were used on a chronic basis or for patients with compromised ocular surfaces (Noecker et al, “Corneal and Conjunctival Changes Caused by Commonly Used Glaucoma Medications” (2004) Cornea 23(5):490-496;

- “The use of low concentrations (0.01% or lower) of BAK appears to be acceptable from both a microbiological and toxicological perspective.” (Peter Edman, *Biopharmaceutics of Ocular Drug Delivery*, (1993) CRC Press, pp. 46-47, and see Easty and Sparrow, above, at p. 10); and

- The “use of preservatives in eye drops should generally be avoided and the formulation of such preparations in single-dose containers is desirable” (Martindale, above, p. 1133).

[242] In addition, as of 2005 a number of commonly prescribed ophthalmic medications had been formulated in preservative-free form, using single-dose containers, including TIMOPTIC (timolol) and ACULAR (ketorolac tromethamine). Another ophthalmic medication was reformulated using a different preservative (Purite) that caused less irritation than BAK: ALPHAGAN (brimonidine). There are no examples in the state of the art where the

concentration of BAK was increased in an ophthalmic medication for the treatment of glaucoma or IOH.

[243] All of this points to a trend away from using BAK, or using as little of it as possible. There is nothing in the literature that supported the idea of increasing the concentration of BAK by a significant amount beyond what was needed to ensure that it provided sufficient preservative to avoid infection.

[244] I should add, however, that the evidence also shows that clinical ophthalmologists in 2005 were prepared to accept the presence of BAK as a "necessary evil" in medications they prescribed for the treatment of glaucoma and IOH. In most other glaucoma medications BAK was in concentrations of 100-150 ppm; it was lower in old LUMIGAN, at 50 ppm. It was higher in latanoprost, at 200 ppm, butas of 2005 the state of the art showed that this higher concentration was partly needed to get latanoprost into solution to avoid white turbidity. Some portion of the BAK complexed with latanoprost in the solution, and therefore the full concentration was not affecting the surface of the eye.

[245] Based on all of this, I find that increasing the amount of BAK in the formulation was contrary to the teaching of the state of the art at the relevant time. With this, I turn to the last element of the inventive concept, which involves using BAK as a penetration enhancer to ensure that the lower amount of bimatoprost in the formulation achieved equal or better IOP reduction than old LUMIGAN.

(3) Achieving Equal or Better IOP Reduction

[246] The third element of the inventive concept is that the new formulation achieve equal or better IOP reduction. Because decreasing the amount of bimatoprost in the new formulation was expected to result in lower IOP reduction, this raises the question whether the state of the art showed that increasing the concentration of BAK would off-set the impact of lowering the amount of bimatoprost. This involves an assessment of the evidence regarding BAK as a penetration enhancer, because that was the mechanism by which a lower amount of bimatoprost could achieve equal or better IOP reduction. In simple terms, if BAK enhanced the penetration of bimatoprost across the cornea, less of the drug would work as well as (or better than) old LUMIGAN because more of it could reach the aqueous humour.

[247] Juno's argument on this stage of the test rests on two pillars. First, it points to the plentiful literature in the state of the art showing that BAK has long been known to be a penetration enhancer. Second, Juno asserts that by 2005 the POSITA knew that other similar glaucoma medications containing BAK were effective, and thus the BAK did not prevent them from penetrating the corneal epithelial barriers, delivering the active ingredients into the aqueous humour.

[248] Both Dr. Morgan and Dr. Alany pointed to the copious literature about BAK as a penetration enhancer. For example, Dr. Morgan referred to a leading ophthalmology text, Adler's Physiology of the Eye, by Kaufman and Alm (10th Edition, 2003), in support of his opinion that the Skilled Ophthalmologist would have known that BAK had been used to improve corneal

permeability. Dr. Morgan indicated that the Skilled Ophthalmologist would have deferred to the formulator regarding the amount of BAK to include in the formulation.

[249] Dr. Alany's report provides a more extensive discussion of the state of the art on this question. He states that penetration enhancers affect the diffusion of a drug across corneal tissues, which are typically the rate-limiting step in ocular drug absorption. Using penetration enhancers is a mechanism to improve ocular bioavailability of the drug. Dr. Alany describes BAK as a "cationic surfactant" which was commonly used as an antimicrobial preservative in eye drops. He cites the Handbook of Pharmaceutical Excipients – a well-known text that all formulators rely on – which states that BAK also functions as an antiseptic, disinfectant, solubilizing agent and wetting agent.

[250] According to Dr. Alany, as of 2005 the Skilled Formulator would have known that BAK had general penetration enhancing properties. In the 1940s, BAK was reported to increase the corneal permeability of carbochol, which Dr. Alany describes as "an old hypotensive drug used to treat glaucoma, as well as to preserve ophthalmic solutions." BAK's penetration enhancement properties are explained by Dr. Alany in the following passage from this expert report:

> This effect is due to BAK's property as a cationic surfactant. A cationic surfactant is a substance with a dual character (hydrophilic head and lipophilic tail) that bears positive charges and can be efficiently adsorbed on materials having negative charges through strong electrostatic charges or charge-charge interactions. This same effect as a surfactant also causes the superficial cell membranes to become diffuse and leaky, resulting in improved paracellular transport of drugs.

[251] Dr. Alany cites a number of sources from the state of the art to support his opinion that BAK was known to act as a penetration enhancer. For example, Edman's Biopharmaceutics of Ocular Drug Delivery (1993) discusses BAK at some length, and states:

> BAK, for example, is an excellent bactericide that also induces increased drug permeation across the cornea, and because of the lack of penetration of this compound beyond the corneal epithelium, BAK has a markedly diminished potential toxicity to internal ocular structures.

[252] Similarly, Mitra's Ophthalmic Drug Delivery Systems (2003) contains a summary of ophthalmic penetration enhancers, and shows that by 2003, BAK was known to have improved the penetration of a wide range of ophthalmic compounds, including: carbachol, timolol, betaxolol, and PGF2α. According to Dr. Alany, routine tests would be required to determine the degree to which BAK would improve the corneal permeability of a specific compound, or the amount of BAK needed to achieve the desired result.

[253] Dr. Alany also refers to Adler's Physiology of the Eye, which states:

> The most commonly used preservative is BAK. The antibacterial action of BAK is based on the detergent property of the compound, which acts to break down bacterial cell walls. These characteristics of a preservative also render the corneal epithelium and endothelium susceptible to damage when they are exposed to these agents… Application of a drop containing 0.01% BAK to the cornea causes an immediate, measurable increase in the permeability of the cornea to fluorescein…

[254] Another widely used text, Duane's Clinical Ophthalmology (2004) referred to research showing that BAK broke down the tight junctions of the epithelial cells and thereby allowed

penetration of compounds. Dr. Alany quoted from Havener's Ocular Pharmacology (1994), which stated that BAK is one of the most popular cationic detergents that was used for the preservation of eye drops and to enhance corneal penetration of drugs. Havener's continues:

> Since the introduction of carbachol in [BAK] in 1942, these 'wetting agents' are known to increase corneal penetration of drugs. This was considered to be a desirable effect that enhanced therapy and was therefore to be sought. The reason for enhanced penetration must be damage to the epithelial cells. Fortunately, they grow back so rapidly as to be completely replaced every 3 days, so damage to them is relatively inconsequential or at least transitory.

[255] According to Dr. Alany, the main point a formulator would take from these texts is that BAK increased corneal permeability and it "should enhance the penetration of many drugs, as its mechanism of action did not seem to depend on the chemical or physical properties of the drug itself".

[256] Dr. Alany bolsters his opinion on BAK as a penetration enhancer with reference to other sources, including articles by Burstein and Higaki, which both report on experiments showing that BAK enhanced corneal permeability (these articles are discussed below). He also refers to other literature as well as the presence of BAK in commercially available ophthalmic products.

[257] Allergan's experts disagreed with their counterparts' opinions, presenting a more nuanced view of the state of the art on BAK as a penetration enhancer. In their view, it was more accurate to state that BAK was known to enhance the penetration of some molecules, but not for ones that are similar to bimatoprost.

[258] The starting point for both Dr. Noecker and Dr. Berkland is that bimatoprost is a lipophilic drug. Because of that, it would penetrate the cornea more easily if the lipophilic epithelium was intact. Anything that disrupted the integrity of the corneal epithelium would be expected to reduce the permeability of bimatoprost across the cornea. In Dr. Noecker's words: "Since BAK is known to damage the corneal epithelium it is counterintuitive that increasing BAK would increase penetration of bimatoprost." On this point, Dr. Noecker cites the Lumigan Medical Review, which he describes as the only available data on the impact of BAK on bimatoprost's efficacy in lowering IOP. This is discussed below.

[259] As with Dr. Alany's evidence on this point, Dr. Berkland's evidence went into more detail from a formulator's perspective. The crux of his opinion on this point is the same as that of Dr. Noecker: that the state of the art only taught the POSITA that BAK would serve as a penetration enhancer for some molecules, and moreover it indicated that BAK would inhibit the efficacy of a lipophilic drug such as bimatoprost.

[260] Beyond these general statements, Dr. Berkland's evidence largely consisted of a systematic review of the literature cited by Dr. Alany, and because this is the central evidence on this point, I will review it in some detail. After a summary of Dr. Berkland's comments on Dr. Alany's report, a more in-depth discussion of three critical pieces of prior art will be undertaken before turning to my analysis and findings on this element.

[261] Dr. Berkland notes that Dr. Alany cites Edman in support of his opinion that "it was well-known that BAK enhances corneal penetration in addition to acting as a preservative." He

disagrees with that statement because in his view, the text does not support such a general statement. Instead, Edman identifies certain molecules that had their penetration enhanced by BAK, while also specifying other molecules for which BAK did not have that effect.

[262] Dr. Alany cited Edman's explanation that BAK's "effect as a surfactant also causes the superficial cell membranes to become diffuse and leaky, resulting in improved paracellular transport of drugs." However, Dr. Berkland points out that "the paracellular pathway is hydrophilic and will favour the penetration enhancement of hydrophilic, as opposed to lipophilic, molecules like bimatoprost."

[263] Edman also discussed the effect of BAK on the permeability of fluorescein, which is strongly lipophilic. According to Dr. Berkland, the Skilled Formulator would appreciate that fluorescein is a diagnostic agent (i.e. a dye), and not a glaucoma drug, and that it is structurally very different than bimatoprost. Fluorescein is also a charged molecule that makes it act more like a hydrophilic drug, in contrast to bimatoprost which is neutral.

[264] Edman cited an article by K. Green, "The Role of Surfactants as Bactericides in Topical Drug Delivery", (1992) 2(1) Journal of Scientific and Technical Pharmacy at page 36. However, Dr. Berkland observes that Green's findings explain that whether BAK will act as a penetration enhancer depends on determining if the molecule is hydrophilic or not. Dr. Berkland's opinion is that Green teaches away from using BAK to increase corneal penetration for lipophilic drugs like bimatoprost.

[265] As regards Dr. Alany's reliance on Mitra, Dr. Berkland states that the Skilled Formulator would understand that the text explains that BAK may enhance penetration in part by opening the tight junctions between cells, and thereby improve paracellular transport. However, that route is hydrophilic, and therefore would not assist with the penetration of a lipophilic drug such as bimatoprost. Dr. Berkland also points out that Mitra explains that the most well-known penetration enhancer to improve paracellular transport is EDTA, but it was not found to act as a penetration enhancer for bimatoprost. Finally, Dr. Berkland notes that Mitra appears only to list drugs that had their penetration enhanced by BAK, including, for example, PGF2α. It does not mention the opposite results for PGF2α isopropyl ester, however, and therefore presents an incomplete picture.

[266] Dr. Berkland notes that Dr. Alany relies on Adler's Physiology of the Eye: Clinical Application, which explains that 100 ppm BAK increased the permeability of the drug fluorescein. He points out that Dr. Alany does not mention the explanation provided by the authors:

> The corneal epithelium provides an initial barrier to penetration with its tight junctions, thereby limiting the absorption of hydrophilic, ionized substances and favouring the penetration of lipid-soluble hydrophobic compounds.

[267] In Dr. Berkland's view, Adler's supports his opinion that opening up the more hydrophilic junctions between the cells with BAK would not enhance the penetration of bimatoprost into the eye. He indicates that Duane's Clinical Ophthalmology, another source cited

by Dr. Alany, confirms this point and does not suggest that BAK could enhance the penetration of a lipophilic molecule like bimatoprost.

[268] As noted earlier, the experts' evidence focused in particular on three pieces of prior art, which will be discussed in greater detail given their importance for the analysis of this part of the test.

[269] The first piece of prior art that merits further discussion is the article by K. Higaki et al, "Estimation and enhancement of in vitro corneal transport of S-1033, a novel antiglaucoma medication" (1996), 132 International Journal of Pharmaceutics 165 [Higaki].

[270] In this article, the authors note the therapeutic possibilities of Prostaglandin F2α ("PGF2 α") compounds but also their adverse effects. They set out to estimate the corneal permeability of a prostaglandin derivative labelled as S-1033, which was reported to be a prostaglandin-derivative antiglaucoma medicine, similar to bimatoprost. The authors also investigate the relationship between corneal permeability and lipophilicity, as well as the effect of BAK on this relationship for prostaglandin derivatives.

[271] The study found that the addition of BAK significantly enhanced the permeability of S-1033. However, the addition of BAK to the S-1033 methyl ester did not improve its permeability. The authors state: "Addition of [BAK] would enhance corneal uptake of S-1033 by modifying the integrity of the corneal epithelium and/or widening the intercellular spaces of the superficial epithelial cell layers" (references omitted). The authors go on to conclude:

> Although [BAK] can improve the corneal penetration of a variety of hydrophilic compounds, the transcorneal transport of the lipophilic prodrug of PGF2α has been reported to decrease in the presence of [BAK] (references omitted).

[272] Dr. Berkland begins by noting the key difference between the two molecules studied in Higaki; he states that S-1033 is more hydrophilic, whereas S-1033 methyl ester is more lipophilic like bimatoprost. He notes that the results from Higaki show that the addition of BAK increased the penetration of S-1033 into the cornea, but resulted in decreased penetration for S-1033 methyl ester. Because of this, Dr. Berkland says that Dr. Alany's comment that Higaki showed that S-1033 had its penetration enhanced by BAK is "quite misleading." He points out that Dr. Alany "fails entirely to refer to the fact that these same authors also studied the penetration effect of S-1033 methyl ester." This is significant, according to Dr. Berkland, because the methyl ester of S-1033 is more like bimatoprost and therefore the data presented by Higaki on it is highly relevant to the POSITA's understanding whether BAK could act as a penetration enhancer for bimatoprost.

[273] Dr. Alany responds by noting that the Higaki statement cited above references the Camber and Edman publication, and his criticisms of Dr. Berkland's analysis of that paper, discussed below, apply with equal force to the conclusions to be drawn from Higaki.

[274] The second key piece of prior art is an article by O. Camber and P. Edman, "Factors influencing the corneal permeability of prostaglandin F2a and its isopropyl ester in vitro" (1987) 37 International Journal of Pharmaceutics 27 [Camber and Edman].

[275] This article reports on experiments investigating factors relating to corneal uptake of PGF2α and PGF2α isopropyl ester. In some of the experiments, BAK was added at a concentration of 0.01%, "in order to simulate a pharmaceutical eye drop solution."

[276] The authors found that BAK increased the corneal penetration of PGF2α, but PGF2α isopropyl ester showed the opposite result. The results reported in this study were dramatic: the 0.01% BAK solution increased the corneal permeability of PGF2α tenfold, whereas it decreased PGF2α isopropyl ester by 50%. Camber and Edman conclude:

> From this study it is clear that the corneal epithelium functions as a barrier for hydrophilic drugs and as the site of activation of prodrugs such as PGF2α esters. It is also evident that agents such as [BAK] can be contraindicated where the drug compound is dependent on an intact epithelium for its conversion to a pharmaceutically active drug.

[277] In Dr. Berkland's view, the key take-away from this article is that the penetration of PGF2α isopropyl ester – which is a lipophilic molecule like bimatoprost – was inhibited with the addition of BAK. Dr. Berkland observes that PGF2α isopropyl ester is lipophilic, with a logP of 3.40, which is quite similar to bimatoprost, which has a logP of 3.2. Camber and Edman also showed that the permeability of PGF2α was increased by the addition of BAK. However, PGF2α is a more hydrophilic molecule.

[278] According to Dr. Berkland, a Skilled Formulator would place particular importance on the results of Camber and Edman, especially the finding that BAK negatively affected the penetration of PGF2α isopropyl ester, because of the similarity between that molecule and bimatoprost.

[279] In reply, Dr. Alany states that such a sweeping conclusion cannot be drawn from Camber and Edman. He says that the authors studied corneal uptake and permeability of PGF2α (the naturally occurring, pharmacologically active form of prostaglandin) and its isopropyl ester, which is a prodrug of PGF2α. Dr. Alany explains that a prodrug is a pharmacologically inactive (or less active) compound that is administered to the body and then converted to an active drug by a physiological or chemical process. He states that among other things, Camber and Edman studied the effect of BAK on the enzymatic hydrolysis of the prodrug.

[280] Based on this, Dr. Alany's opinion is that Camber and Edman shows that the corneal epithelium functions as a barrier for hydrophilic drugs and as the site of activation of prodrugs such as PGF2α methyl esters. He states that the statement that BAK can be contraindicated relates to "formulations where the drug is an ester prodrug (which is not the case for bimatoprost); ester prodrugs are dependent upon an intact epithelium for their conversion by enzymatic hydrolysis to pharmacologically active drugs to aid permeation through the cornea."

[281] Dr. Alany also notes that in another paper by the same authors published in 1987, they demonstrated that the presence of 0.01% BAK enhanced the corneal permeability and uptake of a lipophilic drug 4-fold.

[282] Based on all of this, Dr. Alany's view is that a Skilled Formulator "would treat [Camber and Edman] with caution and would have reservations as to its applicability to bimatoprost." He also points to the fact that both XALATAN and TRAVATAN contain isopropyl esters of PGF2α, along with 200 ppm and 150 ppm BAK respectively. Each of the active ingredients in

these products is a prodrug that would be expected to be hydrolysed by the same enzyme studied in Camber and Edman. The fact that these drugs were commercially approved and widely used would provide comfort to the Skilled Formulator about the fact that 150 or 200 ppm of BAK did not prevent sufficient corneal penetration of the active ingredient. Dr. Alany's opinion is that Camber and Edman did not teach away from the concept that BAK would be useful to enhance the corneal permeability of bimatoprost.

[283] Dr. Alany says that his critique set out above also applies to the Higaki paper. In his view, the flaws he points out in Camber and Edman undermine the conclusion from Higaki, because the authors based their statement about BAK's impact on the penetration of lipophilic compounds on the finding in Camber and Edman.

[284] Allergan filed a sur-reply report by Dr. Berkland, in which he takes issue with Dr. Alany's analysis of Camber and Edman. Specifically, Dr. Berkland disagrees with Dr. Alany on two points: the hydrolysis issue and the prodrug issue.

[285] On hydrolysis, Dr. Alany stated that Camber and Edman "primarily identifies a potential issue with BAK in the specific context where enzymatic hydrolysis of the isopropyl ester (specifically, a prodrug) crossing an intact epithelium is required." Dr. Berkland says that if Dr. Alany's opinion is that the hydrolysis will slow the penetration of bimatoprost into the cornea, this is mistaken because hydrolysis occurs in the cornea only after uptake, not on the outside of the eye. Based on this, Dr. Berkland's opinion is that Camber and Edman shows that the rate of uptake depends on the lipophilicity of the substance. That factor is the key driver of whether the

drug penetrates into the eye, and at what rate. According to Dr. Berkland, one of the reasons why a prodrug may be desirable in this instance is to make the drug more lipophilic to assist in its penetration into the cornea. The key point a POSITA would take from Camber and Edman is that the penetration of the lipophilic PGF2α isopropyl ester into the cornea – a drug similar to bimatoprost – was reduced when BAK was added.

[286] Turning to the prodrug issue, Dr. Berkland agrees with Dr. Alany that bimatoprost is not an "ester prodrug" – it does not have an ester in its structure (it has an amide instead). He disagrees with Dr. Alany's opinion about the significance of this, because the literature at the time taught that bimatoprost was a prodrug and a POSITA would expect it to behave in a similar fashion as PGF2α isopropyl ester. Dr. Berkland points out that the bimatoprost molecule has comparable size, shape and lipophilicity to PGF2α isopropyl ester and both are neutral compounds. Based on these similarities, a POSITA would expect the conclusions from Camber and Edman on BAK's negative effect on the permeability of the PGF2α isopropyl ester would apply equally to bimatoprost. Building on this, according to Dr. Berkland, a POSITA would conclude that BAK would equally be contraindicated for bimatoprost because it was also reported to be a prodrug that hydrolyzes in the cornea.

[287] Finally, Dr. Berkland asserts that Dr. Alany's criticism of Higaki is also flawed, because the authors of that paper interpreted Camber and Edman in the same way as he did in his evidence, namely that BAK can decrease or inhibit the penetration of a lipophilic drug. He also notes that Higaki attributes the reduction in permeability of S-1033 methyl ester to its increased

lipophilicity relative to S-1033 (which is a more hydrophilic prostaglandin). This would equally apply to the expected permeability of bimatoprost.

[288] The third key piece of prior art is referred to as the Lumigan Medical Review. As part of its New Drug Application for old LUMIGAN filed with the FDA, Allergan submitted clinical data from a number of studies for the formulation of old LUMIGAN. The Lumigan Medical Review document in the record includes redacted versions of the studies, together with the comments of the FDA reviewer(s) who examined the document as part of the approval process.

[289] The Medical Review includes reports on the outcomes of a number of different clinical studies. Allergan cited it as the only data available to the POSITA that addressed the specific question of whether bimatoprost had its penetration enhanced or decreased by the addition of BAK.

[290] Among the data in the Medical Review is the 001 Study, which compared the IOP lowering efficacy and safety of different concentrations of bimatoprost (0.003%, 0.01% and 0.03%). The FDA reviewed the 001 Study data and concluded that the peak effect of bimatoprost was found at concentrations of 0.03%.

[291] The Medical Review also sets out the results of the 004 Study, which was a clinical study comparing the IOP lowering effect of different formulations, including 0.03% bimatoprost together with 50 ppm BAK, and a 0.03% bimatoprost formulation with no preservative. This

data measures the mean IOP change from baseline (established at the outset of the study) at each time point. For the purposes of this discussion, the key results are set out in table form below:

	Day 14 Hour 0	Day 29 Hour 0	Day 29 Hour 4	Day 29 Hour 8	Day 29 Hour 12
0.03% NP	-9.4	-8.86	-7.36	-6.81	-7.31
0.03% P	-8.89	-7.95	-7.53	-6.45	-5.92

[292] Just below the graph and table setting out the results of the 004 Study, the FDA Reviewer's Comment states: "There is not a clear separation in IOPs between the active treatment groups until Day 29 Hour 12 when the greatest IOP lowering effect is demonstrated by 0.03% NP [non-preserved]." These results and this comment were the focus of the evidence of the experts.

[293] According to Dr. Noecker, based on the data from the 001 Study, the Skilled Ophthalmologist would expect less IOP lowering with a lower concentration of bimatoprost. He also took particular notice of the final data point in the 004 Study that is referred to in the Reviewer's comment. Dr. Noecker's opinion was that based on this data, the Skilled Ophthalmologist would understand that increasing the concentration of BAK would inhibit, not promote, the penetration of bimatoprost into the eye.

[294] In Dr. Berkland's view, the Skilled Formulator would draw a consistent conclusion from Higaki, Camber and Edman, and the Lumigan Medical Review to the effect that BAK would not act as a penetration enhancer for bimatoprost and, in fact, was more likely to decrease the penetration of bimatoprost into the eye. He points out that the Medical Review contains the only data specific to bimatoprost and the effect that BAK may have on its penetration into the eye. In

his view, the data showed that the addition of BAK was correlated with less IOP reduction as compared with a non-preserved formulation. For this point, Dr. Berkland focused on the results at Day 14 as well as the other results for different time points except the last one. In his opinion, these data show that the addition of BAK does not affect the IOP lowering effect of bimatoprost, because the results for the preserved and non-preserved 0.03% formulations are basically the same. He notes that at the final time point the results diverge, and points to the Reviewer's Comment that there is actually better IOP lowering when BAK is not present.

[295] Neither Dr. Morgan nor Dr. Alany discussed the Lumigan Medical Review in their reports in chief. Juno was granted leave to file reply expert reports, and both experts provided their opinions on this document and their counterparts' views on it.

[296] Dr. Morgan expressed the opinion that the data in the Medical Review was not sufficient to conclude that BAK inhibited the penetration of bimatoprost based on the single point in time on Day 29. Instead, he stated that a reasonable conclusion would be that the concentration of BAK in this clinical study was insufficient to enhance the effect of bimatoprost at a dose of 0.03%. He points to the other data in the table to refute the idea that BAK inhibited the penetration of bimatoprost.

[297] Dr. Morgan summarized his view with the following analogy: if a graduate student had come to him to present these results from their experiment, he would have sent them back to do more experiments to determine whether the single data point was a valid indication of what was actually going on.

[298] For Dr. Morgan, the main conclusion to be drawn from the 004 Study data is that more research is required, to determine whether any trend line can be established beyond the single data point. He also indicated that the demographic data for the study showed an age imbalance in the study groups: 76% of the subjects were over age 65 for the preserved group, whereas only 43% of the subjects in the non-preserved group were in that age bracket. According to Dr. Morgan, this also supports his view that further research was required before drawing any firm conclusions.

[299] For his part, Dr. Alany's opinion was similar to that of Dr. Morgan, namely that the trend from the data showed there was no clear separation in the IOP reduction of the preserved and non-preserved formulations and that a Skilled Formulator would have wanted to see additional data before drawing any conclusions regarding whether BAK inhibited the penetration of bimatoprost. He pointed to another comment by an FDA Reviewer regarding the 004 Study: "This study is limited by its short duration and limited number of patients." Dr. Alany states that the Skilled Formulator "would not have simply abandoned the use of BAK based on this limited data from this study, given the known benefits of using BAK in ophthalmic formulations as described in my First Report." Instead, he says that a Skilled Formulator would have considered increasing the amount of BAK to understand its benefits.

[300] In response, Dr. Berkland denied that he drew any "wide, sweeping conclusion" from the Medical Review data; instead, he said it was consistent with Higaki and Camber and Edman and its results were of particular interest because it was the only prior art document that specifically assessed the penetration of bimatoprost with and without BAK. Dr. Berkland repeated his

assertion that the Medical Review data were consistent with the results reported in other prior art, and provided no motivation to increase the concentration of BAK, much less to increase it four-fold. Dr. Berkland's opinion is that the Medical Review taught away from increasing the concentration of BAK in the formulation, because 50 ppm had been shown to be effective as a preservative in the old LUMIGAN.

[301] This completes the discussion of the evidence, and I now turn to the analysis of this element of the test.

[302] Based on the evidence before me, and considering the submissions of the parties on this point, I find that the state of the art taught that BAK was not expected to be a penetration enhancer for bimatoprost. There is a difference between the state of the art and the inventive concept in regard to using an increased amount of BAK as a penetration enhancer to try to maintain equal or better IOP reduction with a formulation containing less bimatoprost.

[303] First, while it was known that BAK could enhance the penetration of some molecules, I am not persuaded that the art at the time showed that it would do so for all types of substances. I accept Dr. Berkland's evidence that the state of the art showed that BAK could enhance the penetration of hydrophilic substances, by disturbing the epithelium and opening up the hydrophilic pathways between the tight junctions. This is consistent with the evidence of all experts about how hydrophilic substances cross the cornea – by paracellular transport using the watery pathways between cells.

[304] On this point, I find that Juno's experts over-stated the teaching of the state of the art. The fact that BAK can act as a penetration enhancer for some molecules is not disputed; the key question, however, is whether the POSITA would have expected that adding more BAK would enhance the penetration of bimatoprost.

[305] I find that a review of the state of the art research shows that BAK either diminished, or at the least did not enhance, the penetration of lipophilic substances. This is consistent with the results reported in Higaki, Camber and Edman and the Lumigan Medical Review. I accept Dr. Berkland's evidence on this point.

[306] Starting with Higaki, I accept Dr. Berkland's description of the key teachings from this article. While Higaki found that the addition of BAK enhanced the corneal transport of S-1033 (a relatively hydrophilic substance), it did not have the same effect for S-1033 methyl ester. Dr. Berkland added important context by pointing out that the S-1033 methyl ester is a more lipophilic substance (as compared to the parent compound), and it has a logP which is quite similar to bimatoprost. Higaki cites Camber and Edman for the proposition that "[a]lthough [BAK] can improve the corneal transport of a variety of hydrophilic compounds, the transcorneal transport of the lipophilic prodrug of PGF2α has been reported to decrease in the presence of [BAK]…" This is consistent with Dr. Berkland's opinion, and his interpretation of the teaching of Camber and Edman.

[307] Turning to the Lumigan Medical Review, much attention was focused on the Reviewer's comment on the last data point in the graph reporting the results of the 004 Study. I accept the

cautions expressed by Doctors Morgan and Alany regarding the weight to be attributed to this one data point. That said, in my view the other data reported support the conclusion that the addition of BAK did not enhance the penetration of bimatoprost. If anything, the data shows no real effect of the addition of 50 ppm of BAK to a 0.03% bimatoprost formulation as compared with a non-preserved formulation. This data is not consistent with the idea of increasing BAK to enhance the penetration of bimatoprost, and thereby off-set the effect on IOP reduction associated with a substantial reduction in the concentration of bimatoprost. While I accept that more data would have been required to reach a definitive conclusion, the key point for this case is that the data in the Lumigan Medical Review did not teach that adding BAK was likely to increase the penetration of bimatoprost into the cornea.

[308] Furthermore, all of the experts were consistent that the corneal epithelium is lipophilic, and therefore more easily penetrated by relatively lipophilic molecules. There is no debate that bimatoprost is relatively lipophilic, with a logP of 3.2. The evidence shows that the corneal penetration of comparable substances studied in both Higaki (S-1033 methyl ester) and Camber and Edman (PGF2α isopropyl ester) was reduced when BAK was added. This is consistent with the results reported in the Lumigan Medical Review. I find that this is also consistent with what the POSITA would expect, because they would predict that the disruption of the lipophilic corneal epithelium would make it more difficult for a lipophilic substance like bimatoprost to penetrate into the cornea.

[309] Finally, I am not persuaded by Dr. Alany's opinion about the teachings of Camber and Edman regarding the prodrug and hydrolysis issues. Both expert formulators indicated that there

was controversy in the research about whether bimatoprost is a prodrug; neither would express an opinion on the point, beyond stating that it was controversial. As of 2005, however, there were reports that bimatoprost was a prodrug. Second, the relevance of whether hydrolysis begins on contact with the eye (as stated by Dr. Alany) or only on uptake into the cornea (Dr. Berkland's opinion) was not explained by Dr. Alany's evidence.

[310] Turning to the existence of other glaucoma medications on the market as of 2005 that contained both PGF2α isopropyl esters and BAK, while I accept that this would have given rise to questions in the mind of the POSITA, I am not persuaded that the presence of these products – in and of themselves – is sufficient to show no difference between the state of the art and inventive concept.

[311] I have already accepted Dr. Berkland's evidence that at least part of the BAK found in XALATAN complexed with the active pharmaceutical ingredient, and thus was not available to disturb the corneal epithelium. This fact answered at least part of the question about why this drug was successful in penetrating the cornea. In addition, the fact that old LUMIGAN (at 50 ppm) and TRAVATAN (at 150 ppm) were both effective glaucoma medications may have given rise to some fruitful lines of scientific inquiry, but did not show a POSITA that adding more BAK to a formulation with two-thirds less bimatoprost was likely to increase corneal penetration.

[312] None of the research suggests that the higher levels of BAK in these other medications was intended to increase corneal permeability, nor does it support the thesis that this is the

function that BAK actually performed. Absent this, I am not persuaded that the higher levels of BAK in these other products would have shown the POSITA that increasing it for bimatoprost would enhance its penetration.

[313] It is important to put this debate into its proper context. The question at this stage of the analysis is whether there was a difference between the state of the art and the inventive concept. One key part of that is whether adding more BAK to the formulation would be expected to off-set the reduction in bimatoprost, thereby achieving equal or greater IOP reduction. This is vital because IOP reduction was the only known treatment for glaucoma and IOH.

[314] Camber and Edman (like Higaki) showed that the addition of BAK either did not enhance, or actually impeded, the corneal penetration of lipophilic molecules similar to bimatoprost. Dr. Alany never explained whether or how the fact that bimatoprost may be a prodrug, or hydrolysis may occur on contact with the eye, would explain these results. I find this debate to be beside the point, for the purposes of this stage of the analysis of this question.

[315] Finally, I am not persuaded by Juno's submission that by 2005 the existence on the market of PGF2α analogs containing BAK would have inspired a POSITA to increase the level of BAK. At most, this would have suggested a possible line of inquiry. It did not diminish the weight of the state of the art teaching away from increasing BAK, because of its cytotoxic effects on the corneal epithelium, and the evidence showing it did not enhance the penetration of lipophilic molecules.

[316] For all of these reasons, I find that there was a substantial gap between the state of the art and the inventive concept in Claims 16 and 19 of the 691 Patent.

(4) Conclusion on Sanofi Step 3

[317] It is worth returning to first principles: the question under consideration is whether Allergan's patent is invalid because the invention was obvious at the time it was claimed. The purpose of the above analysis has been to assess the inventive concept of the claims in light of the state of the art at that point in time.

[318] This is a precursor to the fourth step in the Sanofi inquiry, which asks whether the differences identified at step 3 would have been obvious to the POSITA or whether they required any degree of invention. Put simply, an inventive concept that was fully canvassed by the existing state of the art is likely to be found to be obvious. In contrast, a significant gap between the state of the art at the time and the inventive concept may point towards an invention that is not obvious. Assessing the differences, if any, between the inventive concept and the state of the art is the task at hand.

[319] I find there were significant differences between the state of the art and the inventive concept. I agree with Allergan's description of these differences:

> First, the prior art did not teach that reducing the concentration of bimatoprost from 0.03% to 0.01% could result in equivalent efficacy. Instead, the prior art taught that the efficacy of 0.01% bimatoprost would be worse. Second, the prior art taught to reduce or eliminate BAK due to toxicity concerns. In contrast, the invention increased the concentration of BAK above the 50 ppm

> that was sufficient to preserve the old formulation. Third, although the prior art taught that BAK could potentially act as a penetration for certain drugs, it taught that BAK would not enhance penetration for a lipophilic compound like bimatoprost. The only prior art that tested bimatoprost with and without BAK showed BAK did not enhance penetration.

[320] With this, we turn to the fourth and final step of the Sanofi analysis.

E. *Step 4 – Obvious to Try*

[321] The fourth step of the *Sanofi* test was expressed in the following way:

> (4) Viewed without any knowledge of the alleged invention as claimed, do those differences constitute steps which would have been obvious to the person skilled in the art or do they require any degree of invention?

[322] The Supreme Court noted that if a patent pertains to an area "of endeavour where advances are often won by experimentation, an 'obvious to try' test might be appropriate" (*Sanofi* at para 68). The jurisprudence has long recognized that pharmaceutical patents is an area where advances are generally the result of experimentation, and so the "obvious to try" test is often applied in cases like this one.

[323] Justice Rennie provided the following important clarifications regarding this step of the test in *Shire* (for ease of reference, all citations have been omitted). First, "[o]bviousness is assessed objectively and purposively, having regard to the problem addressed by the patent."

[324] Second:

> For an invention to be "obvious to try", there must be evidence establishing, on a balance of probabilities, "that it was more or less self-evident to try to obtain the invention". As such, this analysis flows from the identification of the "invention" described by the claim's inventive concept… The "obvious to try" test does not broaden the scope of the obviousness inquiry from a claim-by-claim analysis to an invention-overall analysis''.

[325] Finally, Justice Rennie considered the non-exhaustive factors set out in *Sanofi* that should be considered in assessing whether it is more or less self-evident to try to obtain the invention:

1. Is it more or less self-evident that what is being tried ought to work? Are there a finite number of identified predictable solutions known to persons skilled in the art?

2. What is the extent, nature and amount of effort required to achieve the invention? Are routine trials carried out or is the experimentation prolonged and arduous, such that the trials would not be considered routine?

3. Is there a motive provided in the prior art to find the solution the patent addresses?

[326] A fourth factor was recognized in *Sanofi* (at paras 70-71) and confirmed in subsequent decisions, which is the actual course of conduct that culminated in the making of the invention: see, for example *Teva Canada Limited v Janssen Inc*, 2023 FCA 68 at para 28. Justice Rennie describes this in the following way:

> [107] Beyond the enumerated factors, there are contextual factors that should also be considered, depending on the facts of the case. These contextual factors include but are not limited to the history

> of the invention, how "quickly, easily, directly and relatively inexpensively" it was reached and any "wild goose chases" that were pursued before arriving at the invention… Although these additional contextual factors may not be, on their own, determinative, any that arise alongside the factors enumerated in Sanofi are to be considered and weighed before coming to a conclusion about whether the invention was obvious.

[327] One final point: while each of these factors must be considered, they need not all be met (*Shire* at para 106, citing *Hospira Healthcare Corp v Kennedy Trust for Rheumatology Research*, 2020 FCA 30 [*Hospira*] at paras 89-90).

[328] Juno argues that the invention in Claims 16 and 19 was obvious to try, while Allergan rejects that argument. I will summarize the evidence of the experts, as well as Dr. Chang, and then set out the arguments of the parties, before turning to my analysis of this element.

(1) The Evidence

[329] Dr. Noecker's evidence on this point is grounded in the desire to maintain IOP lowering efficacy. For him, that is the main goal of any formulation for a glaucoma medication. Based on this, he expressed the opinion that because of the hyperemia problem associated with old LUMIGAN, a Skilled Ophthalmologist would have asked a formulator to provide re-formulation options that would lower hyperemia while maintaining the concentration of bimatoprost, because that was what was needed to ensure efficacy of the medication.

[330] Based on the data from the state of the art outlined above, Dr. Noecker stated that the invention in the claims was counterintuitive in all respects. In his view, it would have been

expected that reducing the amount of bimatoprost would result in less IOP lowering efficacy. The state of the art taught away from increasing BAK because of its negative effects on the corneal epithelium, and it was not expected that more BAK would increase the penetration of bimatoprost. For all of these reasons, Dr. Noecker's opinion was that the invention in Claims 16 and 19 was not obvious to try, and if tried, it was not self-evident that it would work.

[331] Dr. Noecker stated that the data from Laibovitz showed that a 0.01% bimatoprost formulation was inferior to old LUMIGAN, and did not result in IOP reduction that was comparable to the best available comparator products on the market at that time. In this regard, he stated that timolol was no longer viewed as the "gold standard" among available medications to treat glaucoma and IOH, and thus the reference to it in Laibovitz is not particularly relevant from a clinical perspective.

[332] For Dr. Noecker, it was important that there were no examples where glaucoma and IOH drugs had been reformulated to reduce the active ingredient and increase the amount of BAK. Instead, such medications had been formulated in preservative-free options, or the active pharmaceutical ingredient [API] was reduced and the amount of BAK was maintained, reduced or replaced. On this point, Dr. Noecker points to BETOPTIC (API reduced by 50%, BAK maintained at 100 ppm); ACULAR (API reduced from 0.5% to 0.4%, BAK reduced from 100 to 60 ppm) and ALPHAGAN (API reduced from 0.02% to 0.015% and BAK replaced with Purite).

[333] Dr. Berkland's evidence largely tracked that of Dr. Noecker. In his opinion, the invention in the Claims was neither obvious nor obvious to try. In addition to the documents from the state

of the art discussed above, Dr. Berkland also noted that developments in the marketplace did not support or encourage the concept of reducing bimatoprost while increasing BAK. Finally, he points to the actual course of conduct of the Allergan team that developed the new formulation, and this is discussed below.

[334] Dr. Chin-Ming Chang, one of the inventors listed on the 691 Patent, also testified for Allergan. I find that Dr. Chang possesses the qualifications of the POSITA Skilled Formulator, as previously defined. He was the lead formulator on the Allergan Enhancement Team from 2003 until the completion of the project.

[335] Dr. Chang provided evidence about the work of the team that developed the LUMIGAN RC 0.01% formulation contained in Claim 16 of the 691 Patent. The first meeting of the Lumigan Enhancement Team ("Lumigan Team") was held February 1, 2022. By that time, the hyperemia problem associated with old LUMIGAN was known. The meeting minutes show that the Lumigan Team discussed a number of formulations that might mitigate the hyperemia problem, including several in which BAK would be replaced with Purite. The minutes show that increasing BAK was not among the options discussed at that time.

[336] Likewise, a number of formulations were prepared and assessed throughout 2002. Dr. Chang provided a document dated June 25, 2002, prepared by his predecessor as lead formulator on this project, which lists a number of formulations designed to reduce hyperemia while maintaining the efficacy of the product. According to Dr. Chang's evidence, maintaining the IOP lowering efficacy of old LUMIGAN was absolutely required by Allergan, because it already had

an effective product on the market (old LUMIGAN) which he described as having “superb efficacy”.

[337] The formulation document sets out the rationale for trying different formulation options, including:

- Cyclodextrin-based – this was meant to shield bimatoprost from the tissue and thereby reduce the hyperemia it caused;

- Refresh liquigel – this was an existing Allergan product with Purite as a preservative which was known to be very mild, and so could be used as a vehicle to deliver the bimatoprost and to minimize potential irritation;

- High calcium, borate-buffered – some research suggested that calcium could play a vasoconstriction function, and it was hoped that narrowing the blood vessels would lessen the hyperemia associated with bimatoprost;

- Castor oil emulsion – similar to the cyclodextrin option, this would minimize contact of bimatoprost with the eye, by emulsifying it into emulsion oil droplets; and

- Gellan gum – this is a hydrogel that could permit a lower concentration of bimatoprost and would delay the release of the bimatoprost into the tissue.

[338] In all of these formulation options, the concentration of bimatoprost was maintained at 0.03%.

[339] None of these approaches worked. Dr. Chang testified that throughout 2002, the Lumigan Team tried fourteen different formulation approaches, but none succeeded in meeting the goals of the project. The Lumigan Team also tried formulating old LUMIGAN in bottles that would deliver a microdrop (ranging from 5, 10, 15 or 20 microlitres) as compared with the marketed product at about 30 microlitres. This approach did not succeed in reducing hyperemia; instead, it reduced the IOP lowering efficacy of the drug.

[340] Formulation work continued throughout 2003, with a particular attention to reformulating bimatoprost with Purite instead of BAK. These efforts ultimately failed because it was found that bimatoprost degraded in the presence of Purite, and thus these formulations lacked the stability necessary for regulatory approval and commercial use. The Lumigan Team decided to abandon its efforts to replace BAK with Purite.

[341] In March 2004, the Lumigan Team developed several formulations of 0.03% bimatoprost with a known penetration enhancer called TPGS (a form of Vitamin E). The intention was to evaluate the effect of TPGS on penetration enhancement of bimatoprost. Five formulations of 0.03% bimatoprost with varying levels of TPGS were prepared, and none of these contained BAK. An additional formulation of 0.03% bimatoprost with 200 ppm BAK was also prepared. These were evaluated against old LUMIGAN as the “control”. The results of this study showed that TPGS decreased absorption. Dr. Chang stated that this was a surprise, because TPGS was a known penetration enhancer. No further efforts were made to assess bimatoprost with TPGS.

[342] In August 2004, the Lumigan Team turned to another penetration enhancer, EDTA. An *in vitro* study was done to determine whether EDTA and BAK may be effective in increasing the penetration of bimatoprost into the eye. Fourteen formulations were prepared and tested, each with 0.015% bimatoprost, as well as 50, 125 or 200 ppm BAK, and either 0%, 0.015% or 0.03% EDTA. The results of this study showed that EDTA did not significantly increase the penetration of bimatoprost. In contrast, the penetration of bimatoprost was enhanced with higher amounts of BAK. Dr. Chang stated that the "results of this study was a surprise to me, and I believe that it was also a surprise to my colleagues."

[343] Dr. Chang also described the work done on or about August 31, 2004, to formulate the compound described in Claim 16 of the 691 Patent. In addition, he described the further testing done by Allergan prior to seeking regulatory approval of the new formulation.

[344] Juno challenged aspects of Dr. Chang's evidence, as discussed below.

[345] Juno's experts stated their opinion that the invention in Claims 16 and 19 was "obvious to try". Dr. Morgan stated that the hyperemia problem associated with old LUMIGAN provided the motivation to try to increase patient compliance by reducing the incidence of hyperemia. For him, any reduction in side effects while maintaining efficacy would have been welcomed by a Skilled Ophthalmologist. In his view, the POSITA would have been aware of Laibovitz, and based on the data reported there would have expected that a formulation with 0.01% bimatoprost would be effective in lowering IOP by 20%. In his opinion, this is a clinically useful result.

[346] Based on that, Dr. Morgan states that there was nothing inventive in arriving at a formulation using 0.01% bimatoprost, as in Claim 16. In addition, a Skilled Ophthalmologist would have expected that using less bimatoprost would reduce the incidence of hyperemia, based on the results reported in Laibovitz, and would have wanted to confirm this with an additional study. Dr. Morgan indicated that because the practical goal of such a study was to obtain a clinically useful treatment, a Skilled Ophthalmologist would have wanted to use a preserved formulation. Given that BAK was the most commonly used preservative, and that it had been approved at various concentrations, the Skilled Ophthalmologist would not have questioned a formulator's recommendation to use BAK at any of the concentrations found in previously-approved commercial products. The choice of BAK concentration would have been left to the formulator.

[347] In Dr. Morgan's view, there was therefore nothing inventive in arriving at an ophthalmic composition comprising 0.01% bimatoprost and 0.02% (200 ppm) BAK. He also stated that there was nothing inventive in using any of the other excipients in the formulation in Claim 16, or in seeking a pH of 7.3, because these were all commonly accepted in existing glaucoma drugs.

[348] Dr. Morgan expressed the opinion that it was obvious to try a formulation using less bimatoprost and more BAK, based on the known efficacy of 0.01% bimatoprost and the use of BAK as a preservative and to improve corneal permeability. In his view, this was all self-evident, as was the expectation that reducing the amount of bimatoprost would have the effect of causing less hyperemia.

[349] While the Skilled Ophthalmologist would not have known in advance whether a formulation using less bimatoprost would have the same efficacy as old LUMIGAN, this could be confirmed through testing which was readily done using the skilled team. In Dr. Morgan's view, such testing was routine. Finally, he stated that the POSITA would be strongly motivated to find a different formulation that delivered clinically effective IOP reduction while reducing the incidence of hyperemia, in order to increase patient compliance. The risks associated with using more BAK in this formulation would have been accepted by the Skilled Ophthalmologist, given the state of the art as of 2005 and the fact that it was the most commonly used preservative found in other glaucoma medications.

[350] Dr. Alany's evidence largely mirrored that of Dr. Morgan, but from the perspective of a Skilled Formulator. In his view, there were a finite number of possible predictable solutions to pursue in arriving at a formulation to develop an effective glaucoma medication with reduced hyperemia. Dr. Alany indicated that reducing the dose of the active ingredient would be the first choice "to address hyperemia head on." Similarly, increasing the amount of BAK was a natural choice to increase the corneal permeability of bimatoprost and improve its bioavailability. Dr. Alany agreed with Dr. Morgan that the choice of other excipients was self-evident, as was maintaining a pH level of 7.3.

[351] If the inventive concept involved comparable efficacy, Dr. Alany's view was that this would be easily confirmed using routine tests and making any necessary adjustments to the formulation.

[352] The prior art provided the motivation to find an effective formulation for treating glaucoma that would also increase patient compliance, according to Dr. Alany. Based on the success of old LUMIGAN in reducing IOP, his view was that the skilled team would have been motivated to refine the formulation of bimatoprost rather than searching for a new drug candidate to replace it. Whatever risks might be associated with using BAK would have been counter-balanced by working within the range of known and approved concentrations found in other comparable products on the market at the time.

[353] Based on all of this, Dr. Alany's opinion is that by March 16, 2005, the differences were obvious to try. He also expressed the opinion that Allergan's course of conduct showed that the work was relatively routine. He noted that by November 2002, Allergan had studied five different concentrations of bimatoprost, and a report on the results of this study dated January 2003 stated: "The results of this dose response study may be useful in testing new formulations of bimatoprost. If the bioavailability of bimatoprost can be improved with a different formulation, it may be possible to use a different concentration and provide similar efficacy with less hyperemia." In his view, Allergan's records show that the work in 2002 and 2003 was focused on developing a new formulation of bimatoprost rather than solving the problem with the existing formulation, and it was only when this did not succeed that it turned to examine penetration enhancers and different amounts of BAK. Once it made this shift, Allergan quickly arrived at the solution found in Claims 16 and 19 of the 691 Patent.

(2) Submissions of the Parties

[354] Juno submits that the problem the inventor set out to solve was reducing the hyperemia associated with old LUMIGAN. That problem was well known, and both Doctors Noecker and Morgan confirmed that lack of patient compliance due to hyperemia was the main drawback limiting the effectiveness of old LUMIGAN. According to Juno, that provided the motivation to the skilled team to search for a different formulation.

[355] As for the differences, Juno argues that there are no new ingredients in the formulation of Claim 16 as compared with old LUMIGAN. The only difference is the reduced concentration of bimatoprost and the increase in BAK. Juno points to Laibovitz as showing the efficacy of less bimatoprost. Juno argues that the results in Laibovitz demonstrated that reducing the 0.03% bimatoprost formulation by two-thirds to 0.01% would reduce the IOP lowering efficacy by only approximately one-third (29.6% vs 20.7%). Further, Juno notes that despite this reduction, the new formulation still delivered better IOP reduction than timolol, which was the "gold standard" comparator for the FDA at the time.

[356] Juno argues that a Skilled Formulator would have naturally considered the use of a penetration enhancer to offset the effect of reducing the amount of bimatoprost; this was taught by the Common General Knowledge. Since BAK was already used in the original formulation, and because it was known to act as a penetration enhancer, Juno submits that increasing the amount of BAK was a natural step. On this point, Juno points to the evidence as of 2005 showing that bimatoprost was absorbed through the sclera, citing Woodward et al, The Pharmacology of

Bimatoprost, (2001) Survey of Ophthalmology, Volume 45, Supplement 4. This suggested that greater uptake through the cornea would enhance its IOP lowering effect, and thus a penetration enhancer was a logical strategy to follow.

[357] In regard to concerns about increasing the amount of BAK, Juno points to the state of the art, including: the presence on the market of effective glaucoma medications with more BAK than old LUMIGAN (including XALATAN at 200 ppm); the absence of regulatory guidance to remove or reduce BAK; and the literature, such as Abelson, which indicated the continued use of BAK was clinically acceptable.

[358] Juno argues that Allergan's reliance on Higaki and Camber and Edman is misplaced, because that research covered specific molecules and did not identify a class of drug for which BAK may not be effective as a penetration enhancer. According to Juno, viewing the state of the art collectively as of 2005 "conveyed the general message that BAK enhances corneal penetration for a wide range of drugs with a concentration dependent effect…" This expectation simply required confirmation by testing increased amounts of BAK with bimatoprost.

[359] Juno points out that the "obvious to try" analysis focuses on what it would take to achieve the alleged invention in the patent. Whereas being "more or less self-evident to try to obtain the invention" is a mandatory requirement of the test, whether or not it is "more or less self-evident that what is being tried ought to work" is simply a factor to be considered.

[360] According to Juno, in this case the motivation to reduce hyperemia was clear. In addition, the general concept of reformulating a glaucoma drug to reduce the amount of the active ingredient to improve patient compliance while maintaining IOP lowering effectiveness was not new. It is simply a specific application of the general principle that all experts endorsed, namely that the best practice was to use the least amount of the active ingredient (and any excipients) needed to achieve the desired effect.

[361] Juno submits that Dr. Noecker's evidence on this point focused on the solution rather than the problem to be solved. While he recognized that the problem with old LUMIGAN was the higher rates of hyperemia, he asserted that there was no motivation to reduce the amount of bimatoprost, despite the fact that he accepted that the bimatoprost was causing the problem.

[362] Furthermore, Juno argues that it was more or less self-evident that what was being tried ought to work. Bimatoprost caused hyperemia, and so reducing it was a logical step. Adding BAK would increase the penetration of the bimatoprost into the eye, thereby producing an effective product. Juno points to the evidence of Dr. Alany that a relatively minimal degree of effort was involved in designing and carrying out the experiments needed to assess whether increasing the amount of BAK would enhance the penetration of bimatoprost. Dr. Morgan also stated that confirming the efficacy of the new formulation would simply involve repeating the experiments in Laibovitz.

[363] As for the actual course of conduct of Allergan, Juno notes that the inventor's evidence was incomplete and omitted key details. Dr. Chang was not a member of the Lumigan Team

from the beginning, and thus could not speak from personal experience about the original work of the group. He was also not aware of several studies and documents that indicate that Allergan was examining the efficacy of different concentrations of bimatoprost as early as April 2002, with the results of the initial dose response study reported by October 2002.

[364] Juno also points out that Dr. Chang was also not aware of the precise formulations used in some of the studies, and acknowledged that his assumption that the only difference was the amount of bimatoprost or BAK was, in fact, incorrect (some of the formulations also contained a surfactant and solubilizer called poloxomer 407). Further, Juno submits that Dr. Chang failed to acknowledge that in March 2004, Allergan had studied the effect of BAK as a penetration enhancer and the results showed that it served to increase the permeability of bimatoprost.

[365] Juno challenges Dr. Chang's statement that he was "surprised" by the results that TPGS and EDTA did not enhance penetration of bimatoprost while BAK had that effect. Juno points out that none of the Allergan documents reflect any similar statements, and the Lumigan Team had been examining the effect of BAK as a penetration enhancer as of March 2004.

[366] Based on all of this, Juno asserts that it has demonstrated that the invention was obvious to try.

[367] Allergan rejects this interpretation. According to Allergan, the legal question at this stage of the analysis is whether there was a specific motivation to arrive at the inventors' solution to the general hyperemia problem. Allergan asserts that it was not self-evident that what was being

tried ought to work and there were not a finite number of solutions. They point to the evidence that the Lumigan Team's expectation was that the inventor's solution would not work.

[368] Allergan underlines the nature and extent of the changes to the formulation of old LUMIGAN reflected in the invention: the amount of bimatoprost is reduced by two-thirds, while the amount of BAK is increased four-fold. The state of the art at the time indicated that reducing bimatoprost would reduce efficacy, and that BAK would not serve as a penetration enhancer for a lipophilic molecule like bimatoprost. The data on the closest analogs to bimatoprost, namely PGF2α isopropyl esters and the methyl ester of S-1033 showed that both had their permeability inhibited by the addition of BAK. In addition, the only study that specifically examined the question – the Lumigan Medical Review – showed no penetration enhancement for bimatoprost when BAK was added. Allergan argues that based on this, it was not self-evident that BAK would work as a penetration enhancer.

[369] Further, Allergan contends that the extent, nature and amount of effort undertaken by the Lumigan Team was extensive. Allergan points out that while Dr. Morgan suggested that the Laibovitz study would need to be repeated to confirm the efficacy of the new formulation, he also criticized that study's methodology and suggested improvements that would be needed to make its results more robust. In addition, although Juno's experts recommended repeating the test disclosed in the Lumigan Medical Review, they also stated it would need to be done over a longer period, with more test subjects and a more robust methodology. Allergan asserts that Dr. Noecker was the only expert with the experience and credentials based on actual involvement in

such clinical trials, and his unchallenged evidence was that such clinical trials are not routine work.

[370] In addition, Allergan notes Dr. Chang's evidence to the effect that the inventors required 2.5 years to arrive at the formulation of Claim 16, and they spent the first two years assessing over 14 different formulations with no clinically useful results. Allergan spent in excess of [redacted] on this project until the filing date of the Canadian patent. Allergan asserts that this expenditure and the history of the actual course of conduct of the inventors shows that it was not self-evident that the new formulation would work.

(3) Analysis

[371] There was no dispute between the parties that the "obvious to try" analysis was appropriate in this case, and I agree that this case involves an area where advances are usually the product of experiments. At the outset, however, it is important to recall that the obvious to try factors are simply factors to consider in the overall analysis, they do not replace or eclipse the overall question on this stage of the test (*Hospira* at para 90). The test to be applied is:

> Viewed without any knowledge of the alleged invention as claimed, do those differences constitute steps which would have been obvious to the person skilled in the art or do they require any degree of invention?

[372] I am not persuaded by Juno's argument that it was more or less self-evident to try the steps that were required to obtain the invention. Bridging the gap between the state of the art and the invention required a degree of inventiveness.

[373] I have previously found that the state of the art showed that reducing the amount of bimatoprost in the formulation was expected to reduce its IOP lowering efficacy. This is consistent with the state of the art, and also with the evidence of the expert formulators. The evidence shows that as a general rule, lowering the API would be expected to reduce the efficacy of the drug, unless other steps were taken to somehow counteract that effect.

[374] Dr. Morgan's evidence was that Laibovitz showed that 0.01% bimatoprost would reduce IOP by 20%, and he stated this was a clinically acceptable result. I have no reason to doubt that a drug delivering a 20% IOP reduction would be clinically useful for an ophthalmologist treating glaucoma or IOH. However, in my view that does not establish that reducing bimatoprost in the formulation was an obvious step to take for the simple reason that a 20% IOP reduction was less effective than the existing Allergan product already on the market and it did not match the results achieved by other competitor products. The inventors' goal was to deliver comparable (or better) IOP lowering efficacy than old LUMIGAN, while also reducing the incidence of hyperemia.

[375] As for increasing the amount of BAK, I have previously found that the state of the art at the relevant time taught away from increasing the amount of BAK. There was no need to increase the amount of BAK to improve the preservation of the formulation; the 50 ppm found in old LUMIGAN had served that function and was approved by the appropriate regulators. Insofar as the goal was to enhance the penetration of the drug into the cornea, there were other tried and tested penetration enhancers that could have been tried (e.g. TPGS and EDTA), but the state of the art did not support the idea that BAK was likely to act as a penetration enhancer for a lipophilic molecule such as bimatoprost.

[376] In this case, it is also appropriate to consider the actual course of conduct of the Lumigan Team that developed the invention. The Lumigan documents make clear that from the outset, the team's goal was to seek to develop a medication that "produces less hyperemia, or improves penetration (lower concentration) or some other quality to develop a better formulation." Clearly, the hyperemia associated with old LUMIGAN was a major concern, and various documents show Allergan's interest in addressing the problem. The documents also confirm that Allergan's other main goal was to maintain the IOP lowering efficacy of their product, because that was viewed as a key point of differentiation with the competition's products.

[377] The evidence is that the Lumigan Team spent over [redacted] over the course of two and one-half years, during which they tried several different approaches using fourteen different formulations. Many of these efforts matched what the expert formulators suggested as possible strategies for improving the effectiveness of ophthalmic medications (e.g. using ointments or gels, or trying to get the drug to penetrate more quickly).

[378] However, none of the team's efforts over this period resulted in a clinically acceptable solution. It was only when the team turned to testing the possible impact of known penetration enhancers that they had any success. Dr. Chang's evidence is that the actual results of these experiments were a surprise, because the penetration enhancers did not increase the amount of bimatoprost that reached the cornea. However, the 200 ppm BAK formulation resulted in significantly greater permeability and eventually was the foundation for the new formulation that is in Claim 16 of the 691 Patent.

[379] All of this evidence shows that the nature and degree of effort involved in achieving the invention was not routine or straightforward. This invention was not reached "quickly, easily, directly and relatively inexpensively" (*Shire* at para 107, citing *Sanofi* at paras 70-71 and *Apotex Inc v Pfizer*, 2019 FCA 16 at paras 46-48).

[380] To summarize on this point, I find:

- Given the differences identified at Step 3, in light of the prior art and without any knowledge of the alleged invention as claimed, the steps required to "bridge the gap" would not have been obvious to the POSITA. They required a degree of inventiveness;

- This is a case where the "obvious to try" test is appropriate, as one of the relevant factors to consider;

- Among the factors I considered on this point, per *Sanofi* at paragraph 69, I find that:

    - It was not more or less self-evident that what is being tried ought to work. There were many possible solutions to the problem to be solved that were known to the POSITA;

    - The extent, nature and amount of effort required to achieve the invention was extensive. The work did not involve routine trials;

    - There was a motive in the prior art to find the solution the patent addresses; and

- Allergan's actual course of conduct shows that it did not reach the invention "quickly, easily, directly and relatively inexpensively".

[381] For all these reasons, I conclude that the invention was not obvious to try.

[382] In summary, I am not persuaded that the 691 Patent is invalid for obviousness. I have found in favour of Allergan's position on each step of the *Sanofi* test, for the reasons set out above.

VIII. Sufficiency of Disclosure

[383] Having found that the 691 Patent is not invalid for obviousness, I now turn to the second issue: is the 691 patent invalid for insufficiency disclosure?

[384] A patent specification must provide enough information to enable the skilled person to practice the invention (subsection 27(3) of the *Patent Act*: *Teva Canada Ltd v Pfizer Canada Inc*, 2012 SCC 60 [*Teva*] at para 51, citing *Pioneer Hi-Bred Ltd v Canada (Commissioner of Patents)*, 1989 CanLII 64 (SCC), [1989] 1 SCR 1623 at 1637-38. See also Teva at paras 55 and 70-71).

[385] The key question is whether, at the end of the patent monopoly a person skilled in the relevant art, "having only the specification [will be able] to make the same successful use of the invention as the inventor could at the time of [the] application" (*Consolboard* at 519, citing

Minerals Separation North America Corporation v Noranda Mines Ltd, [1947] Ex CR 306 at 316).

[386] Juno argues that even if its obviousness arguments are not accepted, the 691 Patent should be found invalid for insufficient disclosure. Juno advanced three arguments on this issue in their written submissions, and added a fourth at the hearing:

- Safety: the Patent failed to disclose information which would allow the POSITA to draw meaningful inferences as to the safety of the invention when it was administered to humans;

- Efficacy: the Patent fails to fully describe the advantage of the 0.01% dose formulations to enable the POSITA to understand its benefits over old LUMIGAN;

- Permeability: the Patent does not adequately disclose that 200 ppm BAK was used to increase ocular permeability of 0.01% bimatoprost; and

- Data based on Rabbit Studies: Juno argues that since Allergan has asserted that data based on rabbit studies cannot be directly extrapolated to the effects on humans, the Patent's disclosures regarding permeability are not sufficient.

[387] These arguments cannot succeed, for the following reasons.

[388] First, all of the experts agreed that the components listed in Claim 16 are well-known, and that BAK and the other excipients are commonly used in ophthalmic formulations. The expert formulators described their work in formulating ophthalmic drops, using similar elements

as those listed in Claim 16. The expert ophthalmologists both said they prescribe eye drops for their glaucoma and IOH patients on a regular basis, in a manner described in Claim 19. None of the evidence suggests a Skilled Formulator would have any difficulty preparing an ophthalmic medication using the components and amounts set out in Claim 16. None of the evidence suggests a Skilled Ophthalmologist would have any difficulty administering that formulation to patients to treat glaucoma or IOH.

[389] The experts acknowledged that the results in the Examples in the 691 Patent demonstrated superior ocular penetration achieved with either 0.03% or 0.015% bimatoprost and 200 ppm BAK as compared with the comparator old LUMIGAN. The results showed that a formulation using significantly less bimatoprost and significantly more BAK than was found in old LUMIGAN achieved comparable or better penetration into the aqueous humour, which is necessary to reduce IOP. I have already found that penetration into the aqueous humour stands as a proxy for IOP reduction, and the results shown in the Examples would lead a skilled person to expect equal or superior IOP reduction based on the amount of the bimatoprost that reached the aqueous humour.

[390] Based on all of this, I find that the 691 Patent, read as a whole, discloses sufficient information to enable a Skilled Formulator to make the formulation in Claim 16, and a Skilled Ophthalmologist to administer it to patients with glaucoma or IOH. That is all that the law requires.

[391] As regards the safety claim, Juno is correct that the 691 Patent does not say anything about the safety profile of the new product. Because it does not claim anything about that, the failure to disclose information relating to it is irrelevant. As was recognized in *Novo Nordisk Canada Inc v Cobalt Pharmaceuticals Inc*, 2010 FC 746 at paragraph 352: "It is well-established in the jurisprudence that the standard required to obtain a patent cannot be equated to that needed to obtain regulatory approval..."

[392] There is no evidence to suggest that the components listed in Claim 16 are so toxic to humans as to give rise to a concern about the overall safety of the formulation, and therefore Juno's reliance on *Eli Lilly Canada Inc v Mylan Pharmaceuticals ULC*, 2015 FC 178 at para 4 does not help their case. To the extent that toxicity of BAK is a consideration, I have previously accepted that BAK has cytotoxic properties and causes harm to the corneal epithelial layer. However, I also note that BAK has been used in other drugs at 150 and 200 ppm, and there is no evidence that BAK at 200 ppm is likely to be toxic to humans.

[393] On efficacy, I find that the specification in the 691 Patent, and in particular the data shown in the examples, is sufficient to establish that the formulation in Claim 16 would deliver comparable or better IOP reduction as compared to old LUMIGAN, and that is all that is required. Although the underlying motivation to develop an enhanced LUMIGAN product was undoubtedly to reduce hyperemia, the 691 Patent does not make any claim in that regard and so the failure to disclose data about the reduction in the incidence of hyperemia is not pertinent.

[394] In addition, there is no requirement that a patent expressly state the problem to be solved or to provide the scientific rationale for why the claimed invention actually works (*Canada LP/Valeant Canada SEC v Generic Partners Canada Inc*, 2019 FC 253 at para 115, citing *Bell Helicopter Textron Canada Limitée v Eurocopter*, 2013 FCA 219 at para 150).

[395] There are two reasons why Juno's sufficiency argument about the failure to disclose that the 200 ppm BAK served as a penetration enhancer cannot succeed. First, the specification in the 691 Patent makes it evident that the bimatoprost formulation with 200 ppm BAK has the greatest permeability into the aqueous humour. The link is clear in the data. Second, a patent does not have to explain how the invention works as long as it explains how to work the invention (*Janssen FC 2021* at para 212, citing *Consolboard* at 525-527).

[396] As to the rabbit studies, I have already discussed the evidence regarding that question. While the data based on rabbit studies cannot be expected to show the precise results that will be achieved in humans, it is regularly accepted as a basis for prediction regarding clinical results, and it is sufficient to tell the POSITA what to expect from the application of an ophthalmic eye drop formulation using less bimatoprost and 200 ppm BAK in the treatment of glaucoma and IOH. That is all the law requires.

[397] Based on the foregoing analysis, I reject Juno's argument that the 691 Patent is invalid for insufficient disclosure.

IX. Conclusion

[398] For these reasons, the Plaintiffs' action will be granted. The 691 Patent is not invalid for obviousness, or for insufficient disclosure.

[399] An order will be issued granting the Plaintiffs' the remedies they seek.

[400] These reasons are confidential. The parties will have seven (7) days to make submissions as to the portions of these Reasons (if any) which should remain confidential. A public version of these Reasons will then follow.

[401] The Plaintiffs are entitled to their costs. The parties were unable to agree on a costs amount, and a Direction will be issued to establish the procedure to be followed with respect to submissions on costs.

JUDGMENT IN T-1994-21

THIS COURT'S JUDGMENT is that:

1. The Defendant's allegations that claims 16 and 19 of Canadian Patent No. 2,585,691 (691 Patent) are invalid for obviousness and insufficiency are dismissed. Claim 16 is valid, and Claim 19 is valid insofar as it refers to administration of the formulation in Claim 16 for the treatment of glaucoma and intra ocular hypertension in humans.

2. The Court declares that the making, constructing, using or selling of Juno Pharmaceuticals Corp. 0.01 w/v bimatoprost solution for ophthalmic administration (the "Juno Product") in accordance with Juno's Abbreviated New Drug Submission ("ANDS") and/or supplementary ANDS for a Notice of Compliance ("NOC") would directly or indirectly infringe at least one of claims 16 and 19 of Patent 691.

3. Costs of the action, including the motion determined herein, are reserved, and will be dealt with in a separate Order.

"William F. Pentney"
Judge

FEDERAL COURT

SOLICITORS OF RECORD

DOCKET:	T-1994-21
STYLE OF CAUSE:	ALLERGAN, INC. AND ABBVIE CORPORATION v JUNO PHARMACEUTICALS CORP
PLACE OF HEARING:	TORONTO, ONTARIO
DATE OF HEARING:	SEPTEMBER 11-27, 2023
REASONS FOR JUDGMENT AND JUDGMENT:	PENTNEY J.
DATED:	DECEMBER 18, 2023

APPEARANCES:

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Douglas Deeth Steffi Tran Nick Wong	FOR THE DEFENDANTS JUNO PHARMACEUTICALS CORP

SOLICITORS OF RECORD:

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