Federal Court  Cour fédérale

Date: 20100426

Docket: T-124-08

Citation: 2010 FC 447

Ottawa, Ontario, April 26, 2010

PRESENT: The Honourable Madam Justice Heneghan

BETWEEN:

PFIZER CANADA INC. and
PHARMACIA ATKIEBOLAG

Applicants

and

THE MINISTER OF HEALTH and
APOTEX INC.

Respondents

REASONS FOR JUDGMENT AND JUDGMENT

I. INTRODUCTION

[1] Pfizer Canada Inc. and Pharmacia Atkiebolag (the "Applicants") apply pursuant to the *Patented Medicines (Notice of Compliance) Regulations*, SOR/93-133 (the "NOC Regulations") for an order prohibiting the Minister of Health from issuing a Notice of Compliance ("NOC") to Apotex Inc. ("Apotex" or the "Respondent"), pursuant to section C.08.004 of the *Food and Drug*

Regulations, C.R.C. 1978, c. 870, until the expiry of Canadian letters patent 1,339,132 (the " '132 Patent"). The '132 Patent is entitled "Prostaglandin Derivatives for the treatment of glaucoma or Ocular Hypertension". A patent list pertaining to 50 microgram/ml ophthalmic solution of Latanoprost and referencing the '132 Patent was submitted to the Minister of Health (the "Minister"). The Minister issued Notices of Compliance to Pfizer for the 50 microgram/ml ophthalmic solution of Latanoprost on various dates, including October 6, 2003. The 50 microgram/ml ophthalmic solution of Latanoprost is marketed in Canada under the registered trade-mark Xalatan®.

[2] This application was commenced following service of a Notice of Allegation (the "NOA") dated March 4, 2008 upon the Applicants. In its NOA, the Respondent alleged that the '132 Patent is invalid on several grounds including anticipation, obviousness, lack of utility, lack of sound prediction, overbreadth, double patenting and lack of sufficiency. The Respondent also alleged that it would not infringe the '132 Patent by producing its version of Latanoprost ophthalmic solution, 50 microgram/ml, hereinafter referred to as "APO-latanoprost".

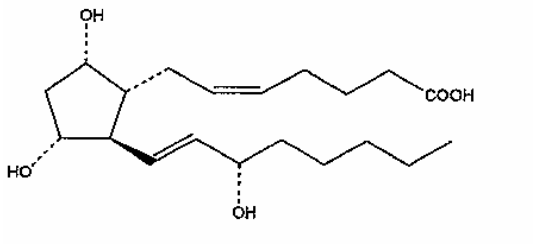
[3] The Minister of Health (the "Minister"), although a party to this proceeding, is not actively participating in it.

[4] Further to an Order made on April 9, 2010, the statutory injunction granted by the NOC Regulations was extended until April 26, 2010.

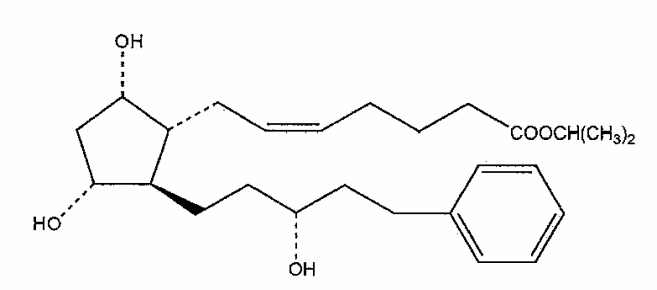
A. The Patent

[5] The '132 Patent application was filed on September 12, 1989. It issued on July 29, 1997. The Patent addresses the use of certain prostaglandin derivatives in the treatment of glaucoma or ocular hypertension.

[6] Prostaglandins are naturally occurring substances found in human and animal tissues that contain 20 carbon atoms and have a molecular structure called "prostanoic acid". The $PGF_{2\alpha}$ is a naturally occurring compound that can be esterified into $PGF_{2\alpha}$ isopropyl ester, also referred to as $PGF_{2\alpha}$ –IE. The chemical composition of $PGF_{2\alpha}$ is as follows:



[7] The Latanoprost compound is a prostaglandin derivative that has the chemical formulation of 13,14-dihydro-17-phenyl-18,19,20-trinor $PGF_{2\alpha}$ isopropyl ester or 13,14-dihydro-17-phenyl-18,19,20-trinor $PGF_{2\alpha}$ -IE. Its chemical structure is as follows:



[8] Latanoprost is made by modifying $PGF_{2\alpha}$ as follows:

i. removing the last 3 carbons of the omega chain ("18,19,20-trinor");

ii. attaching a phenyl ring to carbon 17 ("17-phenyl");

iii. changing the double bond to a single bond between carbon 13 and carbon 14 ("13,14-dihydro"); and

iv. esterifying the carboxylic acid to an isopropyl ester.

[9] The '132 Patent contains 38 claims; however, only Claims 12, 19, 31, 37 and 38 are at issue in this proceeding. Broadly speaking, Claim 19 is a compound *per se* claim that is dependent on Claim 18. Claims 31, 37 and 38 are use claims. Claim 12 is a narrower use claim and is dependent on Claim 1. The relevant claims read as follows:

i. A therapeutic composition for topical treatment of glaucoma or ocular hypertension, containing a prostaglandin PGA, PGB, PGD, PGE or PGF in an amount sufficient to reduce intraocular pressure without causing substantial ocular irritation and an ophthalmologically compatible vehicle, which the omega chain of the prostaglandin has the formula:

(13) (14) (15-24)

C - B - C - D - R_2

wherein

C is a carbon atom (the number is indicated within parenthesis);

B is a single bond, a double bond or a triple bond;

D is a chain with 1-10 carbon atoms, optionally interrupted by hetero atoms O, S, or N, the substituents on each carbon atom being H, alkyl groups, lower alkyl groups with 1 – 5 carbon atoms, an oxo functionality or a hydroxyl group;

R_2 is a ring structure selected from the group consisting of phenyl and phenyl having at least one substituent, said substituent being selected from C_1-C_5 alkyl groups, C_1-C_4 alkoxy groups, trifluoromethyl groups, C_1-C_3 aliphatic acylamino groups, nitro groups, halogen atoms, and phenyl group; or an aromatic heterocyclic group having 5-6 ring atoms, selected from the group consisting of thiazol, imidazole, pyrrolidine, thiopene and oxazole; or a cycloalkane or a cycloalkene with 3-7 carbon atoms in the ring, optionally substituted with lower alkyl groups with 1-5 carbon atoms.

12. An ophthalmological composition according to claim 1, wherein the prostaglandin derivative is 13,14-dihydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$ -isopropylester.

18. 13,14-dihydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$ -alkyl-ester, in which the alkyl group has 1-10 carbon atoms.

19. Compound of claim 18, wherein the alkyl group is isopropyl.

31. The use of 13,14-dihydro-17-phenyl-18, 19,20-trinor-$PGF_{2\alpha}$ -isopropylester in the treatment of glaucoma or ocular hypertension.

37. The use of 13,14-dihydro-17-phenyl-18,19,20-trinor- $PGF_{2\alpha}$ -alkyl-ester, in which the alkyl group has 1-10 carbon atoms for the treatment of glaucoma or ocular hypertension.

38. The use of 13,14-dihydro-17-phenyl-18,19,20-trinor- $PGF_{2\alpha}$ -isopropyl-ester in the treatment of glaucoma or ocular hypertension.

B. The Evidence

[10] Each party submitted affidavit evidence from several witnesses, some of whom provided factual evidence and others who addressed matters of opinion.

i) Applicants' Witnesses

[11] Dr. Wolff is a registered U.S. patent agent and a registered pharmacist in the State of California, United States of America. He obtained a Ph.D. degree in Medicinal Chemistry from the University of California, Berkeley in 1955 and worked as Adjunct Professor of Medicinal Chemistry at the University of Southern California from 1982 to 2002. He was also a member of the faculty of the Residential School of Medicinal Chemistry of Drew University in Madison, New Jersey from 1996 to 2008. He has worked and taught in the fields of medicinal chemistry drug discovery and drug development, both in the pharmaceutical industry and the academic world, for more than 40 years.

[12] Dr. Wolff's mandate was to describe the person of skill in the art ("POSITA"), provide an opinion on the '132 Patent, and to review the opinions expressed by the Respondent's expert witnesses. He said that around September 12, 1989 there were over 40,000 articles published on prostaglandins. Dr. Wolff said that most of the articles provided by the Respondent as prior art have nothing to do with the eye and any teachings on metabolism found in those articles cannot be transferred to the eye field. He also said that Canadian Patent No. 1,208,560 entitled "Use of Eicosanoids and Their Derivatives for Treatment of Ocular Hypertension and Glaucoma" (the " '560 patent"), does not give the POSITA enough directions to make chemical modifications needed to get to Latanoprost.

[13] Discussing the data found in the '132 Patent, he said that using healthy humans gives a sound basis to expect that the drug would work in glaucoma patients because there is no reason to expect substantial differences in the side effects seen between these two groups. He concluded that animal and normal human testing has been and continues to be the standard step-wise process used to evaluate almost all drugs.

[14] Dr. Robert D. Fechtner is a clinical ophthalmologist practising in New Jersey. He is also a professor in the Department of Ophthalmology and Visual Science, New Jersey Medical School, University of Medicine and Dentistry of New Jersey. He has held this position since 2002. He was asked to provide a basic tutorial on the eye and intraocular pressure ("IOP"), glaucoma, ocular hypertension and the treatment of those conditions and to describe the common general knowledge

relative to the treatment of ocular hypertension, glaucoma and prostaglandins as of September 12, 1989.

[15] Dr. Fechtner was also asked to describe the qualifications of the POSITA to whom the '132 Patent is addressed and to state his understanding of the '132 Patent, with reference to Claims 12, 19, 31, 37 and 38 as of July 29, 1997. He was also asked to describe the utility taught by the '132 Patent and whether Latanoprost has utility. He was asked to describe the utility of the '132 Patent and whether Latanoprost exhibits that utility. As well, he was asked to consider whether the specification of the '132 Patent, including Claims 12, 19, 31, 37 and 38 correctly and fully describe, as of July 29, 1997, to the POSITA, the subject matter of the invention and its operation or use as contemplated by the inventor. In addition to reviewing relevant documents, including the '132 Patent, Dr. Fechtner was asked to review certain affidavits filed by the Respondent.

[16] Dr. Johan W. Stjernschantz of Uppsala, Sweden is one of the inventors of the '132 Patent. He addressed the factual background to the discovery of Latanoprost, including the history of other efforts that were made by competitors, seeking the discovery of a drug that would treat glaucoma and ocular hypertension.

[17] As well, Dr. Stjernschantz tendered opinion evidence as to the POSITA as of September 12, 1989, the concept of obviousness of the invention claimed in the '132 Patent having regard to the prior art, the sufficiency of the '132 Patent having regard to the test data in the patent and the evidence tendered by the Respondent, and the utility of the '132 Patent.

[18] I note that Dr. Stjernschantz, as one of the inventors of the ‘132 Patent, is uniquely situated to give evidence about the invention. However, in my opinion, his evidence is to be cautiously treated in respect of issues of claim construction and validity since it is almost impossible for a person with an “interest”, even an intellectual one, to be wholly objective about his own work. In this regard, I refer to the decision in *Emmanuel Simard & Fils (1983) Inc. v. Raydan Manufacturing Ltd.* (2005), 41 C.P.R. (4th) 385 (F.C.).

[19] Dr. Kirk M. Maxey is a medicinal chemist with expertise in the area of prostaglandins with almost 30 years experience in the study and synthesis of prostaglandins. Although he holds a medical degree, he has never practiced as a medical doctor. He is the founder and Chairman of the Board of the Cayman Biomedical Research Institute, a non-profit institute that conducts research in the areas of rare diseases and genetic defects.

[20] Dr. Maxey was asked to give a brief tutorial on prostaglandins. He was also asked to describe the qualifications of the POSITA and to give his understanding of the ‘132 Patent, particularly with regard to Claims 12, 19, 31, 37 and 38 as of July 29, 1997.

[21] Dr. Maxey was also asked to consider whether Latanoprost had been disclosed in the prior art, whether the POSITA would have been led to Latanoprost having regard to the state of the art as of September 12, 1989 and July 29, 1997 and whether the claims in issue are broader than the invention made or disclosed in the ‘132 Patent.

[22] The affidavit of Dr. Maxey disclosed that not only did his company supply the raw prostaglandins used by Dr. Stjernschantz' group, but that no one else had ever requested the compounds that went into the development of Latanoprost and that these base chemicals were not in the main catalogue and were difficult to manufacture.

[23] Dr. Maxey said that he was unaware of any company selling modified 17-phenyl substituted $PGF_{2\alpha}$ as of September 12, 1989. The only people looking for this product were Dr. Stjernschantz and his team at Pharmacia.

[24] Dr. Maxey gave the opinion that Latanoprost was not anticipated by the '560 patent or by NOA Document No. 6 entitled "Effect of Chemical Modifications On The Metabolic Transformation of Prostaglandins". This article was published on December 1, 1976.

[25] Dr. Maxey addressed the issue of esterification of the carboxylic acid of $PGF_{2\alpha}$ and said, in agreement with Dr. Bodor, an expert witness put forward by the Respondent, that this esterification was known as of September 12, 1989. However, he testified that it was also known that other positions could be esterified and sterification was not the solution to the problem of side effects. He concluded that the choice of the four chemical modifications that were made by the inventors was "brilliant".

[26] Dr. Arthur H. Neufeld is a Professor of Ophthalmology and the Head of Laboratory for the Investigation of the Aging Retina at the Northwestern University School of Medicine. He submitted two affidavits on behalf of the Applicants, the first sworn on September 11, 2008 and the second sworn on January 15, 2009.

[27] In his first affidavit, Dr. Neufeld addressed his mandate to give his interpretation on the '132 Patent and whether the Respondent's product APO-latanoprost infringes Claims 12, 19, 31, 37 and 38 of the '132 Patent. In his opinion, the Respondent's product would infringe the specified claims of the '132 Patent.

[28] In his second affidavit, Dr. Neufeld said that he had been asked to explain glaucoma and ocular hypertension and to describe the common general knowledge, as of September 12, 1989, based on his expertise relative to prostaglandins. He was also asked to give his "interpretation" of the '132 Patent as of July 29, 1997 and to describe the qualifications of the POSITA.

[29] The Applicants filed one affidavit of fact, that is the affidavit of Ms. Arshia Ghani, Regulatory Affairs Associate of Pfizer Canada. She deposed to the ownership of the '132 Patent and the issuance of NOCs over a number of years, beginning in 1997.

ii) Respondent's Witnesses

[30] The Respondent filed the affidavits of Dr. Nicholas Bodor, Dr. Cheryl Cullen, Dr. Allan Flach, Dr. Howard Leibowitz, Chrystal Yorke and Ines Ferreira.

[31] Dr. Bodor holds a Ph.D. in organic chemistry and has worked in the fields of pharmochemical research and medical chemistry. He was asked to provide a summary of prostaglandin development and chemistry as of September 12, 1989, as well as his opinion as to whether claims of the ‘132 Patent here in issue are anticipated, by the ‘560 patent and if those claims are obvious.

[32] Dr. Bodor summarized the development of prostaglandins as of September 12, 1989. He also gave a definition of the POSITA. He concluded that that the claims are obvious and anticipated, in light of the ‘560 patent which he observed would direct a person skilled in the art to Latanoprost.

[33] Dr. Cheryl Cullen is an Associate Professor in the Faculty of Veterinary Medicine at the University of Calgary, in Calgary, Alberta. She was asked to provide comments on the animal models and testing described in the ‘132 Patent, and whether these models and tests were sufficient to permit the inventors to predict the behaviour of a new prostaglandin in the treatment of glaucoma in humans.

[34] Dr. Cullen found both the animals and testing insufficient for the purposes of predicting the behaviour of a new prostaglandin in the treatment of glaucoma in humans. Her affidavit sets out various criticisms, including criticism of the sample size and the alleged lack of data.

[35] Dr. Allan J. Flach holds a doctorate in pharmacy and a medical degree. He is an American Board of Ophthalmology certified ophthalmologist and has worked in the field of ophthalmology for more than 30 years. He has been a tenured professor within the Department of Ophthalmology at the USCF Medical Center for 23 years. He was asked to provide a history of prostaglandins, to describe the POSITA and to give his opinion on the animal models and test data found in the '132 Patent.

[36] He concluded that the animal models used were not sufficiently reliable to predict the efficacy and toxicity of prostaglandins in humans. He found that the results of the animal testing could "only provide a general indication of how the prostaglandins will behave in humans". He also concluded that the small number of humans tested was insufficient to support a prediction as to whether the human response to efficacy or toxicity would be favourable or otherwise.

[37] Dr. Howard Leibowitz is a medical doctor with specialized training in ophthalmology. From 1971 to 2002, he served as the Chairman, Department of Ophthalmology, Boston University School of Medicine. He has been recognized by his peers as an expert in external ophthalmic diseases and other diseases. Dr. Leibowitz was asked to provide his opinion on the POSITA, background information on glaucoma, the claims of the '560 patent, whether the '132 Patent discloses sufficient data and information to support a prediction that Latanoprost reduces IOP without causing substantial ocular irritation in humans and whether Latanoprost meets the promise of the patent.

[38] In Dr. Leibowitz' opinion, the '132 Patent claims a treatment for glaucoma and ocular hypertension without substantial ocular irritation and hyperemia. He expressed the opinion that the '560 patent describes and claims "a class of PGE_2 and $PGF_{2\alpha}$ eicosanoid (prostaglandin) derivatives, for the treatment of ocular hypertension without tachyphylaxis". He expressed the opinion that the '132 Patent did not disclose data or results that show that Latanoprost has "surprising or unexpected properties" in light of the teachings of the '560 patent. Finally, he rejected the idea that there was a sound prediction that Latanoprost would "lack" ocular irritation and hyperemia, as side effects in humans.

[39] Finally, the Respondent filed the affidavits of Ms. Chrystal Yorke and Ms. Ines Ferreira.

[40] Ms. Yorke, at the time of swearing her affidavit, was an articling law clerk. She deposed that she attended at the Office of Patented Medicines and Liaison, Health Canada Therapeutic Products Directorate and obtained documents relating to the listing of the '560 patent on the Patent Register. These documents, being copies of Form IV Patent List relating to the '560 patent, are attached as exhibits to her affidavit.

[41] Ms. Ferreira is a legal assistant with the Solicitors for the Respondent. She attached, as exhibit "A" to her affidavit, a copy of a "Patent Expiry Report" for the period January 2003 to December 2003, obtained from the Canadian Patent Register website. This report notes that the Canadian Patent '560 under the brand name "Xalatan", using the medicinal ingredient Latanoprost, expired in July 2003.

[42] Ms. Ferreira also attached a copy of the Respondent's NOA and its Schedules as exhibit "B". The Schedules to the NOA include, in Schedule "B", the documents cited by the Respondent as prior art.

C. The Eye, Glaucoma and Ocular Hypertension

[43] The '132 Patent deals with an ophthalmic solution for treatment of glaucoma and ocular hypertension. The eye is a closed sphere that produces a clear fluid called aqueous humor. Aqueous humor is essential to the functioning of the eye. It conveys nutrients to the eye and removes waste products and contaminants from the eye. Drainage of aqueous humor assists in avoiding an increase in intraocular pressure. Elevated IOP is one of the strongest risk factors for disorders of the eye, including glaucoma and ocular hypertension.

[44] Ocular hypertension means elevated intraocular hypertension in the absence of damage to the optic nerve, according to Dr. Fechtner. Glaucoma, according to Dr. Fechtner, describes a group of disorders that are characterized by damage to the optic nerve that results in loss of vision if the condition is left untreated. Elevated intraocular pressure is one of the strongest risk factors for the development and progression of glaucoma.

[45] There is no cure for glaucoma but both this disease and ocular hypertension can be managed by the reduction of intraocular pressure. According to Dr. Fechtner, this is the only risk factor of these disorders that can be modified by treatment.

[46] Two possible ways of reducing intraocular pressure by the use of drugs are the reduction in the production of aqueous humor and second, an increase in the outflow of aqueous humor.

[47] Successful treatment of glaucoma by the use of drugs requires a high level of patient compliance. Therapies with less frequent dosages are preferred by patients and contribute to patient compliance.

[48] Tolerance of the drug regime is another factor that affects patient compliance. Tolerability of drugs refers to the existence of side effects. Side effects may be systemic, that is occurring throughout the body or local, that is adverse effects occurring in and around the eye. Systemic effects of drugs used to treat glaucoma include worsening of asthma or emphysema. Local side effects include ocular inflammation, that is within the eye, and irritation, that is side effects occurring outside the wall of the eye.

[49] Conjunctival hyperemia, that is redness of the eye, may also be a local side effect. Conjunctival hyperemia can be experienced with or without irritation.

[50] Prior to the advent of Latanoprost, other drugs were on the market for the treatment of glaucoma and ocular hypertension. According to the evidence of Dr. Neufeld and Dr. Fechtner, these drugs included timolol maleate, epinephrine and acetazolamide which caused side effects, including burning, hyperemia, tingling, and stomach upset. Further, more serious systemic effects of these drugs were blood disorders, cardiac arrhythmia, asthma, emphysema and death.

II. ISSUES

[51] The following issues arise from this application:

i. How should the claims in issue be construed?

ii. Will the Respondent's drug infringe the '132 Patent?

iii. Are any of the Respondent's allegations of invalidity justified, as follows:

(a) double patenting

(b) anticipation;

(c) obviousness;

(d) lack of utility;

(e) lack of sound prediction;

(f) overbreadth.

III. DISCUSSION AND DISPOSITION

[52] The parties filed a considerable amount of evidence in relation to this proceeding. I will not refer to all of the evidence contained within the record but instead will base my conclusions upon

that evidence which I found to be most relevant, credible and reliable. I have not ignored evidence which is not specifically mentioned.

A. Nature of This Proceeding

[53] This application seeks to prohibit the issuance of a NOC to the Respondent for its product which contains Latanoprost. The Applicants challenge the Respondent's NOA on the grounds that the allegations of invalidity of the '132 Patent are not justified.

[54] A NOC grants marketing approval for drugs in Canada. It is issued by the Federal Government, indicating that all requirements have been met pursuant to the Food and Drug Regulations for the protection of public health and safety. The NOC Regulations authorize owners of existing patents for pharmaceutical products to file a "patent list" relative to those products for which they hold a NOC. The NOC Regulations refer to the person filing such a list as the "first person". In this case, the Applicants are the "first person".

[55] The framework of the NOC Regulations allows generic drug manufacturers to rely on prior approval of related pharmaceutical products in applying for marketing approval of their generic form of the products. Manufacturers who produce the same drug may file an application for a NOC that refers to and relies on the fact that prior approval has been granted for the brand-name version of the drug. Such a manufacturer is known as the "second person" and that is the Respondent's status.

[56] The NOC Regulations prohibit the Minister of Health from issuing a NOC until all relevant product and use patents in the earlier approved medicine, as described in the patent list, have expired. Consequently, a second person must either wait until patent expiry before receiving a NOC or it may submit a NOA to the Minister with its new drug submission.

[57] The NOC Regulations require service of the NOA upon the first person. Section 5 sets out the grounds upon which a NOA is to be based. Briefly, the NOA must assert either that the first person is not the patentee, that the patent is expired or invalid, or that it would not be infringed if a NOC were issued.

[58] Following service of the NOA, the Minister may issue a NOC to the second person, unless the first person avails of its right, pursuant to section 6(1) of the NOC Regulations, to seek an order from the Federal Court prohibiting the Minister from issuing the NOC. Any such step must be taken by the first person within 45 days after receipt of the NOA and once such a proceeding is commenced, the issuance of a NOC to the second person is stayed for a maximum period of 24 months.

B. Burden of Proof

[59] Before addressing the specific aspects of this case, I will briefly address the jurisprudence applicable to the burden of proof and the question that must be answered in a NOC proceeding. It is well-established that the burden of proving that the second person's, that is, Apotex's, allegations are not justified is on the person seeking the Prohibition Order, Pfizer. Pfizer must establish, on a

balance of probabilities, that Apotex's allegations are not justified. Apotex must put its allegations "in play" through its NOA. However, once that has been done, Pfizer bears the burden of proving that such allegations are not justified, on a balance of probabilities: see *Eli Lilly and Co. v. Nu-Pharm Inc.* (1996), 69 C.P.R. (3d) 1 (F.C.A.), *Merck Frosst Canada Inc. v. Canada (Minister of National Health and Welfare)* (1994), 55 C.P.R. (3d) 302 (F.C.A.) and *SmithKline Beecham Pharma Inc. v. Apotex Inc.*, [2001] 4 F.C. 518 (T.D.), aff'd (2002), 291 N.R. 168 (F.C.A.).

[60] Second, the Court must determine whether Apotex's allegations of invalidity are justified or not. In *Pharmacia Inc. v. Canada (Minister of National Health and Welfare)* (1994), 58 C.P.R. (3d) 209 (F.C.A.) ("*Pharmacia*") the Federal Court of Appeal commented upon the standard to be applied to this type of proceeding, at page 216:

> ...these proceedings are not actions for determining validity or infringement: rather they are proceedings to determine whether the Minister may issue a notice of compliance. That decision must turn on whether there are allegations by the generic company sufficiently substantiated to support a conclusion for administrative purposes (the issue of a notice of compliance) that the applicant's patent would not be infringed if the generic's product is put on the market…

[61] In *SmithKline*, Justice Gibson considered the evidentiary burden in proceedings under the NOC Regulations where invalidity of a patent is alleged. At paragraphs 14 to15 he wrote the following:

> Against the foregoing, I conclude that while an "evidential burden" lies on Apotex to put each of the issues raised in its notice of allegation "in play", if it is successful in doing so, the "persuasive burden" or "legal burden" then lies with SmithKline. Assuming Apotex to be successful in putting the issue of validity of the '637

patent "in play", SmithKline is entitled to rely on the presumption of validity of the patent created by subsection 43(2) of the Act.

The "persuasive burden" or "legal burden" that lies with SmithKline in the circumstances described in the preceding paragraph is, however, impacted by the nature of the proceeding here before the Court. In *Merck Frosst Canada Inc. v. Canada (Minister of National Health and Welfare)*, [(1994), 55 C.P.R. (3d) 302 (F.C.A.)] Mr. Justice Hugessen, for the Court, wrote at pages 319-20:

> As I understand the scheme of the regulations, it is the party moving under s. 6, in this case Merck, which, as the initiator of the proceedings, has the carriage of the litigation and bears the initial burden of proof. That burden, as it seems to me, is a difficult one since it must be to disprove some or all of the allegations in the notice of allegation which, if left unchallenged, would allow the Minister to issue a notice of compliance…
>
> …
>
> In this connection, it may be noted that, while s. 7(2)(b) [of the Regulations] seems to envisage the court making a declaration of invalidity or non-infringement, it is clear to me that such declaration could not be given in the course of the s. 6 proceedings themselves. Those proceedings, after all, are instituted by the patentee and seek a prohibition against the Minister; since they take the form of a summary application for judicial review, it is impossible to conceive of them giving rise to a counterclaim by the respondent seeking such a declaration. Patent invalidity, like patent infringement, cannot be litigated in this kind of proceeding.

Thus, the burden on SmithKline is only to disprove the allegations in the notice of allegation, not to justify declarations of validity and infringement or conversely to negative claims for declarations of invalidity and non-infringement.

[62] The burden lies on Pfizer, as the Applicants, to refute the allegations set forth by Apotex in its NOA dated March 4, 2008. Like any plaintiff or applicant, Pfizer has the overall legal burden of proof. Apotex, as the Respondent, has an obligation to put the allegations set out in its NOA in play.

[63] The present proceeding is a summary proceeding pursuant to the NOC Regulations and the *Federal Court Rules,* SOR/98-106 (the "Rules") governing applications for judicial review. A finding of invalidity or infringement in the context of this type of proceeding is not determinative of that issue in any subsequent action; see *Pharmacia* at page 216.

Issue 1: Construction of the '132 Patent

[64] According to the direction given by the Supreme Court of Canada in its decisions in *Whirlpool Corp. v. Camco Inc.* (2000), 9 C.P.R. (4th) 129 (S.C.C.) and *Free World Trust v. Électro Santé Inc.* (2000), 9 C.P.R. (4th) 168 (S.C.C.), before addressing the issues of infringement and invalidity, the Court must first construe the patent.

[65] Claims construction must be approached in an informed and purposive manner, with close regard to the purpose and intent of the authors. Information is to be gained from the patent as a whole in order to determine the context in which the claims are to be considered. The role of experts is to provide assistance, if necessary, relative to the technical meaning of the words and concepts used in the claims; see *Whirlpool* at paragraphs 51 and 52. In construing the claim, the Court should be neither harsh nor benevolent but approach the claim with a mind willing to understand.

[66] The ‘132 Patent specification gives an overview of disorders of the eye derived from elevated IOP, discloses the results if the eye disorder is left untreated, and defines the formulae to determine IOP levels. The specification goes on to discuss the current state of the art available at the time the patent application was filed as well as the available research activity undertaken in the use of prostaglandins. Finally, the specification discloses the solution that the invention solves as well as some of the preferred derivatives and preferred methods of preparing, testing, using and applying the invention.

[67] The ‘132 Patent is governed by the provisions of the *Patent Act*, R.S.C. 1985, c. P-4, (the “Act”). The provisions of the Act that pertain to patents applied for prior to October 1, 1989, are called “Old Act Patent”. The claims are to be construed from the date of issue, that is July 29, 1997. The ‘132 is an “Old Act Patent”.

[68] The Applicants and the Respondent made submissions on the issue of claims construction. The Applicants argued that claims construction should follow the steps outlined by the Supreme Court of Canada recently in its decision in *Sanofi-Synthelabo Canada Inc. v. Apotex Inc.* (2008), 298 D.L.R (4^{th}) 385 (S.C.C.) at para. 76.

[69] The Respondent submits that the claim in issue should be construed as addressing the abolition of side effects in the chronic treatment of glaucoma by the use of the compound described

in Claim 19 of the ‘132 Patent. Further, it argues that the promise of the patent is chronic use of the compound.

[70] As noted earlier, Claims 12, 19, 31, 37 and 38 are in issue in this proceeding. Broadly speaking, Claim 19 is a compound *per se* claim. Claims 12, 31, 37 and 38 are use claims, with Claim 12 limited by reference to Claim 1.

[71] In *Pfizer Canada Inc. v. Canada (Minister of Health)*, [2009] F.C.J. No. 1659 (F.C.) (Q.L.), I construed Claims 12, 19, 31, 37 and 38 of the ‘132 Patent, the same claims that are in issue here. I am not persuaded by the evidence submitted by the Respondent nor by its arguments that the construction of these claims should differ from what I have already said and my prior construction will apply here, too.

[72] Claim 19 reads as follow:

> 19. Compound of claim 18, wherein the alkyl group is isopropyl.

[73] This claim is for the chemical compound described in Claim 18. Claim 18 reads as follows:

> 18. 13,14-dihydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$ -alkyl-ester,
> in which the alkyl group has 1-10 carbon atoms.

[74] I construe Claim 19, having regard to Claim 18 as being a chemical compound with isopropyl as the alkyl group. The isopropyl used as the alkyl group has three carbon atoms.

[75] Claims 12, 31, 37 and 38 are use claims and I construe them as such. Claim 12 refers to Claim 1 and accordingly, can be read as follows:

i. A therapeutic composition for topical treatment of glaucoma or ocular hypertension, containing a prostaglandin PGA, PGB, PGD, PGE or PGF in an amount sufficient to reduce intraocular pressure without causing substantial ocular irritation and an ophthalmologically compatible vehicle, which the omega chain of the prostaglandin has the formula:

(13) (14) (15-24)

C - B - C - D - R_2

wherein

C is a carbon atom (the number is indicated within parenthesis);

B is a single bond, a double bond or a triple bond;

D is a chain with 1-10 carbon atoms, optionally interrupted by hetero atoms O, S, or N, the substituents on each carbon atom being H, alkyl groups, lower alkyl groups with 1 – 5 carbon atoms, an oxo functionality or a hydroxyl group;

R_2 is a ring structure selected from the group consisting of phenyl and phenyl having at least one substituent, said substituent being selected from C_1-C_5 alkyl groups, C_1-C_4 alkoxy groups, trifluoromethyl groups, C_1-C_3 aliphatic

acylamino groups, nitro groups, halogen atoms, and phenyl group; or an aromatic heterocyclic group having 5-6 ring atoms, selected from the group consisting of thiazol, imidazole, pyrrolidine, thiopene and oxazole; or a cycloalkane or a cycloalkene with 3-7 carbon atoms in the ring, optionally substituted with lower alkyl groups with 1-5 carbon atoms.

12. An ophthalmological composition according to claim 1, wherein the prostaglandin derivative is 13,14-dihydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$ -isopropylester.

[76] The claim for use in Claim 12 is limited by the reference in Claim 1 to the reduction of intraocular pressure "without causing substantial ocular irritation".

[77] Claim 31 provides as follows:

31. The use of 13,14-dihydro-17-phenyl-18, 19,20-trinor-$PGF_{2\alpha}$ -isopropylester in the treatment of glaucoma or ocular hypertension.

[78] I construe this to be a claim for the use of the compound in Claim 19 in the treatment of glaucoma or ocular hypertension. Glaucoma and ocular hypertension are disorders of the eye, according to the evidence of the expert witnesses.

[79] Claim 37 provides as follows:

37. The use of 13,14-dihydro-17-phenyl-18,19,20-trinor- $PGF_{2\alpha}$ -alkyl-ester, in which the alkyl group has 1-10 carbon atoms for the treatment of glaucoma or ocular hypertension.

[80] I construe this to be a claim for the use of the compound claimed in Claim 19 for the treatment of glaucoma or ocular hypertension.

[81] Claim 38 provides as follows:

38. The use of 13,14-dihydro-17-phenyl-18,19,20-trinor- $PGF_{2\alpha}$ -isopropyl-ester in the treatment of glaucoma or ocular hypertension.

[82] I construe this to be another claim for the use of the compound claimed in Claim 19 in the treatment of glaucoma or ocular hypertension. It is identical to Claim 37 with a difference in the spelling of "isopropylester", a hyphen is included in Claim 38.

[83] Since this is an Old Act Patent, the operative date for claims construction is the date of issuance of the '132 Patent, that is July 29, 1997. In this regard, I refer to the decision in *Janssen-Ortho Inc. v. Novopharm Ltd.* (2006), 57 C.P.R. (4th) 6 (F.C.), aff'd (2007), 59 C.P.R. (4th) 116 (F.C.A.), leave to appeal to S.C.C. refused, [2007] 3 S.C.R. xii.

Issue 2: Infringement

[84] The Respondent alleges that its product will not infringe the '132 Patent because the '132 Patent claims an old use for an old compound. This kind of allegation is known as the "Gillette Defence" on the basis of the decision in *Gillette Safety Razor Co. v. Anglo-American Trading Co. Ltd.* (1913), 30 R.P.C. 465 (H.L.) at 480 to 481 where the House of Lords said the following:

> …The defence that "the alleged infringement was not novel at the date of the plaintiff's Letters Patent" is a good defence in law, and it would sometimes obviate the great length and expense of Patent cases if the defendant could and would put forth his case in this form, and thus spare himself the trouble of demonstrating on which horn of the well-known dilemma the plaintiff had impaled himself, invalidity or non-infringement.

[85] The Gillette Defence has been raised in many cases in Canada but has rarely been successful. One exception to that trend is the decision in *Eli Lilly Canada Inc. v. Apotex Inc.*(2009), 75 C.P.R. (4th) 165 (F.C.), at paras. 60 to 64, where the Court, per Justice Hughes, found that the product to be produced by the respondent would not be different from that produced by the process of a prior art patent and in theory, the respondent would infringe the patent in issue in the proceedings before him. However, he found that the product of that earlier patent anticipates the product of the patent in issue and consequently, the claims in issue were invalid.

[86] In my opinion, the availability of the "Gillette Defence" depends upon the determination of the many allegations of invalidity raised by the Respondent. This means that if the allegations of anticipation and obviousness fail, this Gillette Defence must also fail.

[87] Dr. Neufeld addressed the issues of infringement on behalf of the Applicants. He referred to the description of the Respondent's product as set out in the NOA as follows:

> APO-latanoprost (latanoprost) is an ophthalmic solution that is meant to be used topically as eyedrops for the reduction or treatment of IOP in patients that have open-angle glaucoma or ocular hypertension.

[88] In his affidavit, he said that the active pharmacological ingredient in APO-latanoprost is 13, 14-dihydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-isopropyl ester which is Latanoprost as set out in Claim 19 of the '132 Patent.

[89] Dr. Neufeld reviewed the five claims of the '132 Patent that are in issue and tendered the opinion that the Respondent's product will infringe each claim. Claim 12 of the '132 Patent claims an ophthalmological composition containing Latanoprost as described in Claim 19. He also reviewed the use claim in Claims 31, 37 and 38, in comparison with APO-latanoprost, and concluded that the use claim will be infringed by the Respondent's product.

[90] The disposition of the allegation of non-infringement by the Respondent, then, depends upon the assessment of the allegations of invalidity that the Respondent advances.

[91] The Regulations that apply here are the ones as they stood prior to the modifications which came into force on October 5, 2006 since Pfizer's NOC was granted before October 5, 2006.

Issue 3: Invalidity

[92] The Respondent advanced several grounds of invalidity against the '132 Patent, as follows: double patenting, anticipation, obviousness, lack of utility, lack of sound prediction, overbreadth and lack of sufficiency.

i) Double Patenting

[93] The Respondent alleges that the '132 Patent is invalid for double patenting and refers in this regard to the '560 patent. This patent was issued on July 29, 1986. The '560 patent is owned by the Trustees of Columbia University in the City of New York, New York, United States of America.

[94] The '560 patent is not owned by the Applicants. Further, the claims in the '560 patent are different from those in the '132 Patent. In these circumstances, I am not persuaded that the Respondent has established that the '132 Patent is invalid on the grounds of double patenting.

ii) Anticipation

[95] Two distinct requirements must be met in order to prove anticipation, that is disclosure and enablement. The Supreme Court of Canada addressed these requirements in its decision in *Sanofi*. Adopting the approach taken by Lord Hoffmann in the decision of the House of Lords in *Synthon B.V. v. SmithKline Beecham plc*, [2006] 1 All E.R. 685 (H.L.), Mr. Justice Rothstein said the following at paragraph 25 of *Sanofi*:

> He explains that the requirement of prior disclosure means that the prior patent must disclose subject matter which, if performed, would necessarily result in infringement of that patent, and states, at para. 22:

> If I may summarise the effect of these two well-known statements [from *General Tire* and *Hills v. Evans*], the matter relied upon as prior art must disclose subject matter which, if performed, would necessarily result in an infringement of the patent. . . It follows that, whether or not it would be apparent to anyone at the time, whenever subject matter described in the prior disclosure is capable of being performed and is such that, if performed, it must result in the patent being infringed, the disclosure condition is satisfied.

> When considering the role of the person skilled in the art in respect of disclosure, the skilled person is "taken to be trying to understand what the author of the description [in the prior patent] meant" (para. 32). At this stage, there is no room for trial and error or experimentation by the skilled person. He is simply reading the prior patent for the purposes of understanding it.

[96] Once the element of disclosure has been addressed, the Supreme Court in *Sanofi* instructed that the second step, that is enablement, is to be considered only if the prior element of disclosure is satisfied. In this regard, I refer to paragraph 26 of *Sanofi* where the Supreme Court said the following:

> If the disclosure requirement is satisfied, the second requirement to prove anticipation is "enablement" which means that the person skilled in the art would have been able to perform the invention (para. 26). Lord Hoffmann held that the test for enablement for purposes of anticipation was the same as the test for sufficiency under the relevant United Kingdom legislation. (Enablement for the purposes of sufficiency of the patent specification under the Canadian *Patent Act*, s. 34(1)(b) of the pre-October 1, 1989 Act, now s. 27(3)(b), is not an issue to be decided in this case and my analysis of enablement is solely related to the test for anticipation. The question of whether enablement for purposes of sufficiency is identical in Canada is better left to another day.)

[97] In short, the disclosure requirement is met when a single document discloses subject matter that, if performed, would necessarily result in infringement. If there is more than one possible result, there is no disclosure. Further, the requirement of disclosure is not met when the prior art teaches a broad class and the invention is for a specific member of that class; see ***Sanofi, Synthon*** and ***Pfizer Canada Inc. v. Canada (Minister of Health)*** (2008), 67 C.P.R. (4th) 23 (F.C.A.), at para. 83 ("***Pfizer 2008***").

[98] Any patent application filed and any patent issuing from it must comply with subsection 27(1) of the Act which outlines the relevant date to assess the state of the art. In this proceeding, it is two years before the Canadian filing date of the application. The filing date for the '132 Patent is September 12, 1989 under the Act and consequently, anticipation is based on a date on or before September 12, 1987. Subsection 27(1) of the Act provides:

27. (1) Subject to this section, any inventor or legal representative of an inventor of an invention that was (a) not known or used by any other person before he invented it, (b) not described in any patent or in any publication printed in Canada or in any other country more than two years before presentation of the petition hereunder mentioned, and (c) not in public use or on sale in Canada for more than two years prior to his application in Canada, may, on presentation to the Commissioner of a petition	27. (1) Sous réserve des autres dispositions du présent article, l'auteur de toute invention ou le représentant légal de l'auteur d'une invention peut, sur présentation au commissaire d'une pétition exposant les faits, appelée dans la présente loi le « dépôt de la demande », et en se conformant à toutes les autres prescriptions de la présente loi, obtenir un brevet qui lui accorde l'exclusive propriété d'une invention qui n'était pas : a) connue ou utilisée par une autre personne avant que lui-même l'ait faite; b) décrite dans un brevet ou dans une publication imprimée au Canada ou

setting out the facts, in this Act termed the filing in the application, and on compliance with all other requirements of this Act, obtain a patent granting to him an exclusive property in the invention.	dans tout autre pays plus de deux ans avant la présentation de la pétition ci□après mentionnée; c) en usage public ou en vente au Canada plus de deux ans avant le dépôt de sa demande au Canada.

[99] The Respondent cited many articles of prior art. All documents with a date on or before September 12, 1989, the filing date, have been reviewed. No document listed in the prior art disclosed the chemical composition of Latanoprost as defined in the '132 Patent for the treatment of glaucoma or ocular hypertension as further discussed below.

[100] In its NOA, the Respondent referred to several pieces of prior art. Its expert witnesses addressed some of this prior art, including two articles by E. Granstrom and the '560 patent.

[101] The first Granstrom article is entitled "Metabolism of 17-phenyl-18,19,20-trinor $PGF_{2\alpha}$ in the Cynomolgus Monkey and the Human Female". It was accepted on December 16, 1974 and published in January 1975; it was NOA Document No. 5. The second Granstrom article, NOA Document No. 6, was published on December 1, 1976.

[102] The '560 patent was issued on July 26, 1986.

[103] Dr. Bodor opined that both the Granstrom articles and the ‘560 patent anticipate Latanoprost. He said that the Granstrom articles described an active species of Latanoprost, disclosed the benefits of reducing the 13,14-double bond to a single bond, and demonstrated that the oxidation of the 15-OH position to the corresponding ketone occurs extremely quickly.

[104] Dr. Bodor and Dr. Leibowitz took similar stances with respect to the ‘560 patent, saying that this patent disclosed Latanoprost as having promising therapeutic profiles with respect to treating ocular hypertension without causing significant side effects and that isopropyl esters of $PGF_{2\alpha}$ derivatives are the most preferred.

[105] Dr. Bodor also addressed other pieces of prior art, that is an article by B.J. Magerlein, G. L. Bund, F.H. Lincoln and G.A. Youngdale entitled “Synthesis of 17-Phenyl-18,19,20-Trinorprostaglandins”, published in January 1975, NOA Document No. 3, and an article by Dr. Bito entitled “Comparison Of The Ocular Hypotensive Efficacy of Eicosanoids and Related Compounds”, published February 1984, NOA Document No. 17. He offered the opinion that according to the Magerlein article, a POSITA would know to substitute a phenyl ring onto the omega chain of a $PGF_{2\alpha}$ prostaglandin for the purpose of improving its metabolic profile and overall corneal permeability. The Bito article taught that esters of $PGF_{2\alpha}$ compounds and derivatives, especially the isopropyl ester, were more readily absorbed in the body. He expressed the opinion that all the molecular changes in the ‘132 Patent were already known to the POSITA as disclosed in the prior art.

[106] Furthermore, Dr. Bodor said that the Granstrom article, NOA Document No. 6, disclosed an active species form of Latanoprost as an observed metabolite.

[107] Dr. Maxey, Dr. Fechtner and Dr. Neufeld, expert witnesses on behalf of the Applicants, disagreed with the opinions expressed by the Respondent's expert witness. Dr. Maxey considered the opinions regarding the anticipatory effect of NOA Document Nos. 3 and 17, the Granstrom articles, the '560 patent, and other NOA documents. He said the opinion of both Dr. Bodor with respect to the prior art documents demonstrate a hindsight approach and further, that many of these documents have nothing to do with the eye. He said that the Granstrom articles do not disclose the isopropyl compound and the '560 patent does not disclose or enable the POSITA.

[108] Having regard to the conflicting evidence given by the expert witnesses for the Applicants and the Respondent, and having reviewed the documents in question, I am satisfied that none of the documents relied upon by the Respondent disclose the chemical composition of Latanoprost as defined in the '132 Patent for the treatment of glaucoma or ocular hypertension. There is not a single prior publication that discloses all the information that is necessary, for practical purposes, to perform the claimed invention without the exercise of any inventive skill.

[109] In the hearing, the Respondent spent a lot of time addressing the issue of anticipation by reference to the '560 patent. Arguments were made about the "broad" anticipation afforded by the '560 patent. However, the Respondent advanced refinements on the anticipation argument by submitting that inclusion of the '560 patent on the Form IV Patent list by the Applicants was an

"admission" that the '560 patent disclosed Latanoprost and accordingly, that the '560 patent anticipated the '132 Patent.

[110] Additionally, in the hearing, Apotex argued that the only defence of the '132 Patent was a selection patent against the '560 patent as the genus patent. The Respondent amplified the theme of selection patent status of the '132 Patent in further submissions that were made on January 22, 2010 following the decision of Mr. Justice O'Reilly in *Eli Lilly Canada Inc. v. Novopharm Ltd.* (2009), 78 C.P.R. (4th) 1 (F.C.). I will first address the Respondent's submissions concerning the effect of the inclusion of the '560 patent on the Form IV Patent List filed, at some point, by the Applicants.

[111] The Respondent's argument as to the effect on including a drug on the Form IV is enough to establish invalidity of the subject patent on the grounds of anticipation. The subject patent here is the '132 Patent and the reference is the '560 patent.

[112] Unfortunately, however, the Respondent cites no jurisprudence in support of its position. In several decisions, the Federal Court and the Federal Court of Appeal have said that a challenge to the inclusion of a patent on the Patent List is to be made by way of a motion pursuant to subsection 6(5) of the Regulations and not by way of submissions upon an application for a prohibition order. In this regard, I refer to the decisions in *Wyeth Canada v. Ratiopharm Inc.* (2007), 58 C.P.R. (4th) 154 (F.C.), aff'd (2007), 60 C.P.R. (4th) 375 (F.C.A.); *Ferring Inc. v. Canada (Minister of Health)*, 55 C.P.R. (4th) 271 (F.C.) and *Solvay Pharma Inc. v. Apotex Inc.* (2008), 64 C.P.R. (4th) 246 (F.C.).

[113] While I understand that the Respondent is not directly challenging the inclusion of the ‘560 patent on Form IV of the Patent List but rather the effect of such inclusion, I am not prepared to accept the arguments of the Respondent, that such inclusion is *per se* evidence of anticipation, in the absence of jurisprudence in support of that submission.

[114] I turn now to the Respondent’s submissions about the characterization of the ‘132 Patent as a selection patent. According to the Respondent, the only defence available to the Applicants to the allegation of anticipation, was to claim that the ‘132 Patent was a selection patent arising from the genus patent, that is the ‘560 patent.

[115] The Applicants did not make this assertion but chose to defend against the allegation of anticipation on other grounds.

[116] In addressing the decision of Justice O’Reilly in *Eli Lilly* the Respondent reviewed the facts. In that case, the innovator drug manufacturer, Eli Lilly Inc., had unsuccessfully sought a prohibition order in respect of Canadian Patent No. 2,041,113 (the “ ‘113 patent”). Mr. Justice Hughes, the applications judge, found that the ‘113 patent was not a valid selection patent of the ‘1,075,687 (the “ ‘687 patent”). Novopharm began making the drug that was the subject of the ‘113 patent and Eli Lilly brought an infringement action.

[117] In disposing of the infringement action, Justice O'Reilly found that the '113 patent was not a valid selection patent selected from the '687 patent even if the '113 patent were inventive in the "pharmaceutical sense". At paragraph 47 of his Reasons, he said:

> As discussed, the earlier '687 patent covered olanzapine, as well as a large number of other related compounds. By contrast, the '113 patent deals with olanzapine alone. In these circumstances, patent law considers the '113 to be a "selection patent". A selection patent is valid if it discloses to the public something new and useful in exchange for a further monopoly on the already-patented compound. In other words, the question is whether the selected compound truly represents an invention that merits a separate and free-standing monopoly. An "invention" under s. 2 of the *Patent Act* is a "new and useful . . . composition of matter, or any new and useful improvement in any . . . composition of matter". Just as with any other kind of patent, then, a selection patent must disclose an invention. What sets selection patents somewhat apart is that the inventor must disclose an invention over and above what was disclosed in the prior patent – the "genus" patent – covering the selected compound.

[118] Justice O'Reilly concluded that Eli Lilly had not found unexpected or special qualities that would justify a fresh monopoly but had only conducted routine testing. The patent was an invalid selection patent and anticipated by the '687 patent. Since he found that the '687 patent was an invalid selection patent, there was no need to consider the requirements for anticipation or double patenting. The Court found no inventive step when addressing the issue of obviousness.

[119] The Respondent argues that a similar analysis and result arise in the present case. It frames the question as being whether the '132 Patent could validly claim Latanoprost even though the '560 patent had disclosed and claimed a genus that includes Latanoprost.

[120] Apotex argues that the *Eli Lilly* decision stands for the proposition that in addressing anticipation, the Court can conclude that the later patent, here the ‘132 Patent, is not a valid selection patent from the ‘560 patent because it did not describe an invention, over and above what had been previously disclosed.

[121] In reply to the arguments, the Applicants relied on a recent decision of the Court of Appeal of England and Wales in *Dr. Reddy’s Laboratories (UK) Ltd. v. Eli Lilly and Co. Ltd.*, [2010] R.P.C. 9 (C.A.) which is an appeal from the dismissal of an application for revocation of the Eli Lilly patent for the compound olanzapine, Patent EP No. 0454436 (the “ ‘436 patent”). The challenge to the ‘436 patent was by reference to a previous British patent 1,533,235 (the “ ‘235 patent”) that was also owned by Eli Lilly. The ‘235 patent claims a large class of compounds, not all of which are tested or disclosed in the patent.

[122] The ‘436 patent claimed a drug for the treatment of schizophrenia. The compound showed surprising and unexpected properties as compared to other related compounds. The ‘436 patent disclosed animal and early clinical tests and the results. The ‘235 patent shows 15 examples of the preparation of 15 specific compounds. The specification did not disclose specific properties or experimental data on any of the compounds.

[123] The drugs available on the market for the treatment of schizophrenia, that is clozapine and chlorpromazine, had severe side effects, for example involuntary movements of the body or face, chronic distortion of posture, suppression of white blood cells and even death. Until 1990, it was not

known how clozapine worked to avoid some of the bad side effects found when patients used chlorpromazine.

[124] The ‘436 patent was attacked for lack of novelty, obviousness and insufficiency as compared to the ‘235 patent.

[125] The Court rejected the anticipation attack and concluded that there was no individualized description or preferred embodiment of olanzapine in the ‘235 patent by which the skilled person would be able to produce the compound.

[126] In dealing with the obviousness attack, the Court said that a selection patent must show a surprising characteristic that is peculiar to the group. It went on to say that the ‘235 patent was almost useless and no guide to the skilled person for any particular compound because it gave no reliable basis on the teaching and, or, use of any compounds found within its very large class.

[127] The Court also said that the fact that Eli Lilly owns both patents does not change the principles to be applied in deciding whether the teaching of a more recent patent is novel and non-obvious over an earlier patent. At paragraph 115, the Court said:

> …The analysis and outcome must be the same if the 235 patent were claimed and owned by someone wholly unconnected to Lilly, or indeed if the teaching of 235 was in an article published in an academic journal…

[128] The Applicants rely on this recent decision of the U.K. Court of Appeal in response to the Respondent's arguments about the Respondent's reliance on the relevance and applicability of the recent decision of Justice O'Reilly. They submit that the decision in *Dr. Reddy* is consistent with the approach taken by the Supreme Court of Canada to the issue of obviousness, in *Sanofi*. In both instances, the Courts found that the possibility of performing every permutation of compounds set out in a prior patent is still not enough to show anticipation. In the present case, the Applicants do not admit that the '560 patent is a genus patent and they do not assert that the '132 Patent is a selection patent.

[129] Indeed, the Applicants argue that the issue is not before the Court and should not be entertained. However, insofar as the Respondent raises the issue in the context of its allegation of anticipation and in view of the Applicants' substantive response to the arguments of the Respondent, in the face of recent jurisprudence, I will consider the submissions of both parties.

[130] I agree with the position advanced by the Applicants, in response to the merits of the issue. I note that here, the Applicants are the licensees, not the owners, of both the '132 Patent and the '560 patent. The '560 patent expired in July 2003 and now forms part of the general prior art.

[131] There is no evidence in the record before me that the Applicants claim ownership of the '560 patent. They did not assert that the '132 Patent is a selection patent and I decline the Respondent's invitation that I make such a finding. In my opinion, it is beyond the jurisdiction of this Court to advance an allegation that has not been made by the parties, that is that the '132 Patent

is a selection patent of the ‘560 patent. The jurisprudence is clear that allegations in a prohibitive proceeding are to be made, in clear terms and in a timely manner, by the parties. In this regard, I refer to the decision in *AB Hassle v. Canada (Minister of National Health and Welfare)* (2000), 7 C.P.R. (4th) 272 (F.C.A.).

[132] I agree with the Applicants that the decision in *Dr. Reddy* follows the decision in *Sanofi*. The proper approach here is to apply the principles of *Sanofi* and look within the ‘560 patent to see if it anticipates the ‘132 Patent, to ask whether the ‘132 Patent is made obvious by the ‘560 patent and finally, to ask whether the ‘132 Patent has utility as compared to the ‘560 patent as prior art and as compared to all other prior art cited by Apotex.

[133] The legal test to establish anticipation requires the second person to show both disclosure and enablement in an anticipatory publication. The Court needs to consider the question of enablement if the prior publication meets the requirements of disclosure. That threshold has not been met in this case.

[134] The Respondent has not shown that any prior art anticipates the compound claimed in Claim 19. It is not necessary for me to discuss the matter of enablement.

iii) Obviousness

[135] In *Sanofi*, the Supreme Court of Canada set out the prevailing test for obviousness in Canada. This requires the Court to consider the following elements:

(a) identify the skilled person to whom the patent is addressed and the state of the art known to that person;

(b) identify the inventive concept in the claims, having regard to the disclosure if the claims do not expand on that concept;

(c) determine the differences between what was previously known and the inventive concept in the claims; and

(d) determine if those differences would be obvious without the benefit of hindsight.

[136] If the "obvious to try" test is appropriate, Justice Rothstein in *Sanofi* identified four additional but non-exhaustive factors to consider under the fourth step:

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

(b) 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?

(c) Is there a motive provided in the prior art to find the solution the patent addresses?

(d) What is the course of conduct followed in arriving at the invention?

(1) <u>The Person of Ordinary Skill in the Art and the Common General Knowledge</u>

[137] There is really no dispute between the parties that the POSITA could be a medicinal or organic chemist or a pharmacologist, holding at least a Bachelor's degree, with some familiarity with prostaglandins and the ophthalmological field, as well as a medical doctor specializing in ophthalmology. The qualifications of the POSITA were addressed by Dr. Bodor, Dr. Leibowitz, Dr. Flach, Dr. Fechtner, Dr. Wolff and Dr. Maxey.

[138] The relevant common general knowledge of the POSITA would include all of the prior art that was submitted by the Respondent. The experts for both parties agreed that prostaglandins have the potential to reduce IOP and that reduction of IOP was disclosed in the prior art. The Applicants point out that the POSITA believed prostaglandins caused side effects such as hyperemia and irritation in the eye.

[139] The Respondent disagreed and alleged that the '560 patent discloses no or very little irritation occurring in the eye. These points were addressed by Dr. Fechtner, Dr. Flach, Dr. Leibowitz, Dr. Neufeld and Dr. Stjernschantz. The relevant common general knowledge would include awareness of the types of drugs on the market at the filing date of the '132 Patent, that is September 12, 1989.

[140] The Applicants repeatedly emphasized on the fact that Dr. Stjernschantz, as one of the inventors, was awarded the Proctor Medal at the ARVO Conference in 2000. Their emphasis upon the grant of this award for Dr. Stjernschantz' work with prostaglandins, including the invention of

Latanoprost, undoubtedly illustrates achievement and professional respect from peers and others working in the field of ophthalmology.

[141] However, receipt of this award *per se* is not dispositive of the legal issues of obviousness and utility. These issues are subject to distinct legal tests in Canada. While the evidence about the Proctor Medal is interesting and forms part of the background, it is not a determinative answer to the allegations of invalidity that are in play here.

[142] With respect to the issue of the relevant common general knowledge of the POSITA, the Applicants' experts generally concurred that as of September 12, 1989 for Old Act Patent that the POSITA would know that there was no available medication that contained a prostaglandin for the treatment of glaucoma or ocular hypertension.

[143] At that time, that is as of September 12, 1989, the state of the art was a drug called timolol that had to be administered to each eye between two and four times per day for the rest of a patient's life since glaucoma is a chronic condition that requires continuing treatment.

[144] Both Dr. Neufeld and Dr. Fechtner addressed that point in their affidavits. As well, timolol causes systemic side effects such as cardio arrhythmia, asthma and emphysema. There were other drugs on the market, such as acetazolamide, that were effective in treating glaucoma or ocular hypertension with similar side effects to timolol, but none contained prostaglandins.

(2) The Inventive Concept

[145] The Applicants claim that the inventive concept of the claims in issue is the use of Latanoprost to reduce IOP in the treatment of glaucoma or ocular hypertension without causing substantial ocular irritation.

[146] The Respondent asserts that the inventive concept is the addition of the 17-phenyl ring. It submits that this was known and consequently cannot be inventive.

[147] I am persuaded by the evidence of the Applicants, that is the evidence of Dr. Fechtner and Dr. Maxey. Dr. Fechtner, at paragraphs 113 to 115 of his affidavit, said that he is satisfied that the '132 Patent, in comparison with the prior art, "correctly and fully" describes the invention. Dr. Maxey, at paragraphs 70 to 74 of his affidavit, said that the POSITA, even a highly skilled POSITA, would not have been led to Latanoprost.

[148] Prostaglandins, according to both Dr. Maxey, are naturally occurring molecules and are found in infinite combinations naturally. Synthetic types can be made with an infinite number of molecular attachments.

[149] It is either inconclusive or not clearly shown that prostaglandins, other than Latanoprost at that time, did not cause substantial ocular irritation to the extent that another type of prostaglandin was a viable option, except the fact that no other drug was on the market at that time**.** None of the affidavits filed on behalf of both the Applicants and the Respondent conclusively show that there

was another prostaglandin compound ready to be used as a drug on the market with good patient compliance since the side effects were so high as documented in the prior art. Pfizer and Apotex agreed that prostaglandins were a promising area to explore due to the reduction in IOP. However, as of the filing date, the IOP promise could not be separated from the side effects. More exploration was needed to conquer side effects and irritation.

[150] As of September 12, 1989, the general consensus was that prostaglandins were a promising area to explore in terms of IOP reduction but more work was required, since the possibility of patient non-compliance was high, due to the side effects of hyperemia, irritation, burning and other intolerable reactions. The body of conflicting evidence, for example, NOA Doc. 58 Bito Article "Prostaglandins, Old Concepts and New Perspectives", August 1987, NOA Doc. 9 Canadian Patent 986,926 and NOA Doc. 21 Canadian Patent 1,208,560 does not show that the problem of side effects had been solved.

(3) Differences Between the "State of the Art" and the Inventive Concept of the Claim.

[151] As of September 12, 1989, the state of the art would have been the other medicines on the market that were used to treat glaucoma or ocular hypertension. Those medicines are timolol, epinephrine, acetazolamide and pilocarpine.

[152] Latanoprost, a synthetic prostaglandin that was used to treat IOP without substantial ocular irritation, would be different from the state of the art in September 1989 since it is the first

marketable prostaglandin drug. The side effects of Latanoprost, in comparison with those of timolol, are less serious since they were restricted to ocular irritation that is not substantial. In other words, the side effects did not lead to patient non-compliance.

(4) Are these steps obvious to the skilled person or do they require a degree of invention?

(A) Is it self-evident that what is being tried ought to work?

[153] The evidence submitted by the witnesses for both parties shows that as of September 12, 1989, those working in the ocular field wanted to find any type of prostaglandin that would work well enough to be a marketable drug in any area of medicine. Many people were publishing articles describing experimental and theoretical data, thereby creating a vast bibliography, numbering in the thousands of documents about prostaglandins. According to Dr. Maxey, Dr. Stjernschantz, Dr. Flach, Dr. Bodor and Dr. Neufeld, it was easy to find a document pointing in one direction and several others that gave different conclusions.

[154] Finally, it is noteworthy that an almost infinite number of changes can be made to the natural prostaglandin, in this case the naturally occurring $PGF_{2\alpha}$. Furthermore, a POSITA making molecular changes to $PGF_{2\alpha}$-IE could not predict the result, since subtle changes in the addition or removal of molecules from its structure can result in major changes of biological activity.

[155] On these grounds, it would not have been obvious that what is being attempted, that is the chemical structure of Latanoprost, would work.

> *(B) What is the extent, nature and amount of effort required to achieve the invention? Are routine trials conducted or is the experimentation long and arduous, such that the trial would not be considered routine?*

[156] The parties tendered conflicting evidence on this point. Dr. Stjernschantz, on behalf of the Applicants, deposed that the synthesis of prostaglandin analogs was difficult and time-consuming. Experimentation was conducted to find the modification for $PGF_{2\alpha}$ that would yield the desired pharmacological benefits. Of course, Dr. Stjernschantz was more experienced than the POSITA and he had the advantage of having worked with Dr. Bito who was very prolific and one of the most knowledgeable researchers in this field.

[157] Dr. Bodor, Dr. Flach and Dr. Cullen, witnesses on behalf of the Respondent, concluded that Latanoprost was obvious, in light of the prior art. They said that the testing that was performed was routine and inadequate and they question the reliability of the data recorded in the ‘132 Patent relative to that testing.

[158] Testing results shown on pages 18 to 22 and 25 to 29, that is Tables III to VI of the ‘132 Patent disclose test results on animals and healthy humans where Latanoprost demonstrates how it works in that it lowers IOP while having minimal irritative effects. The ‘132 Patent discusses why

certain animals were used as well as the grading used to compare compounds. The test results disclose dosage levels and the grading scale.

[159] Tables III to VI show comparative tests on Latanoprost and other compounds to determine the required outcomes. More specifically, the results on page 29 are from a test of Latanoprost in some healthy human volunteers and show a reduction in IOP over time wherein there is no reported occurrence of side effects such as hyperemia or ocular irritation as discussed on page 21. Table III is a compound comparative test to show the degree of ocular irritation in cats.

[160] Table IV compares the degree of conjunctival hyperemia for different compounds in rabbits, Table V compares the IOP reducing effects of different compounds in monkeys and cats. Table VI uses healthy humans to show IOP reducing effects for various compounds. The tests were criticized by the Respondent's expert witnesses as failing to provide enough "experimental protocols" for the POSITA to reproduce the experiments.

[161] In spite of the conflicting opinions from the experts for the Applicants and the Respondent, I find the evidence adduced by the Applicants to be more persuasive. I am satisfied from the evidence of Dr. Stjernschantz, in particular as set out in paragraphs 40 to 44 of his affidavit, that the POSITA following a similar course of conduct that may encompass routine experimentation, using the common general knowledge and prior art, and acting in a manner similar to that followed by Dr. Stjernschantz, would not obtain the same results.

[162] Indeed, a competitor who performed experiments that were compared to those that had been performed by Dr. Stjernschantz recorded a different conclusion about the viability of using synthetic $PGF_{2\alpha}$ compounds. In this regard, I refer to the paper written by D. F. Woodward et al entitled "Prostaglandin $F2_{\alpha}$ Effects on Intraocular Pressure Negatively Correlate with FP-Receptor Stimulation", published August 1989, NOA document 107.

(C) Is there a motive in the prior art to find the solution that the patent addresses?

[163] As stated above, many people wanted to find a marketable drug using prostaglandins for the treatment of glaucoma and ocular hypertension. Prostaglandins had been identified by prior art as having great efficiency in the reduction of IOP. However, prior to the discovery of Latanoprost, the general consensus was that the irritative effects of prostaglandins could not be adequately removed in order to provide for a useable product. In my opinion, these considerations show that there was a motive to find something else.

(D) What is the course of conduct that was followed in arriving at the invention?

[164] The mixing and reacting of chemicals was used, along with experimentation on animals and humans, in order to obtain data for analysis. The results of the testing are set out in Tables III, IV, V and VI. The tables address testing in cats, rabbits, monkeys or cats and humans, respectively.

[165] The difference here, between the Applicants and its competitors, is in the consolidation of the data, the analysis of the data obtained and the conclusions drawn from the experimentation which was done.

(5) Conclusion on Obviousness

[166] I find that Latanoprost would not have been obvious to the ordinary skilled person**.** I conclude that the allegation of obviousness is not justified.

iv) Lack of Utility

[167] The date for determining utility for an Old Act Patent is the filing date, that is September 12, 1989.

[168] The Applicants rely on the evidence of Dr. Neufeld and of Dr. Stjernschantz to support the claim that the patent has utility. The Respondent relies on allegations of lack of sound prediction more than on a lack of utility, and depends on the evidence of Dr. Flach and Dr. Leibowitz in this regard.

[169] The Applicants refer to the evidence of Dr. Neufeld, Dr. Stjernschantz, Dr. Fechtner and Dr. Maxey to show that the ‘132 Patent has utility.

[170] The Applicants' witnesses, that is Dr. Neufeld and Dr. Stjernschantz, say that Latanoprost shows a reduction in ocular irritation. As the witnesses assert, Claim 12 only refers to a reduction of IOP without substantial ocular irritation. That does not refer to the elimination of all side effects.

[171] Further, the patent itself shows utility. I refer to pages 7 and 8 where the patent demonstrates what the invention is, by stating the use for the treatment of glaucoma or ocular hypertension where the irritating effects are reduced and treatment is given with 1 or 2 drops per eye.

[172] Example 9 on page 16 of the '132 Patent shows how to prepare Latanoprost. Page 22 of the patent demonstrates what the invention is by stating that IOP is lowered with minimal side effects. Page 23 shows the chemical structure of Latanoprost, again what the invention is.

[173] Pages 18 to 22 and pages 25 to 29 disclose test results on animals and healthy humans. The use of Latanoprost demonstrated the reduction of IOP with minimal irritative side effects. Finally, the claims in issue disclose Latanoprost.

[174] The '132 Patent demonstrates utility, discloses what the invention is and how it works, as claimed. Furthermore, the disclosure requirements are met as of the issue date. Disclosure can be assessed against documents published between September 12, 1989 and July 29, 1997. Dr. Fechtner referred to studies that were done comparing Latanoprost to timolol and discussing the effectiveness of Latanoprost. These articles were attached as exhibits to his affidavit.

[175] In the result, I am satisfied that the ’132 Patent offers the public a useful choice from what was offered as the state of the art at the time of filing the patent application and considering the prior art that was available to the POSITA.

v) Lack of Sound Prediction

[176] The doctrine of sound prediction was reviewed by the Supreme Court of Canada in *Apotex Inc. v. Wellcome Foundation Ltd.*, [2002] 4 S.C.R. 153. At paragraph 46, Justice Binnie said that where the invention is for a new use for an old product, the utility that is required for patentability must either be demonstrated or a sound prediction based on the information and expertise then available.

[177] The doctrine of sound prediction has three elements:

i. there must be a factual basis for the prediction;
ii. the inventor must have as the date of the patent application a “sound” line of reasoning from which the desired result can be inferred from the factual basis;
iii. there must be proper disclosure.

[178] The date from which sound prediction is to be considered is the filing date of the patent application, that is September 12, 1989. In this regard, see *Aventis Pharma Inc. v. Apotex Inc.* (2005), 43 C.P.R. (4th) 161 (F.C.), aff’d (2006), 46 C.P.R. (4th) 401 (F.C.A.).

[179] While I have found that the ‘132 Patent has utility, I will address the issue of sound prediction utility because the Respondent has alleged that the ‘132 Patent fails due to lack of sound prediction.

[180] The date and the example of the ‘132 Patent provide a sound line of reasoning and disclosure. Page 16 of the patent discloses how to make Latanoprost. Page 23 shows a diagram of the Latanoprost molecule. Pages 21 to 22 and 29 disclose test results in healthy humans. Pages 25 to 29 disclose test results where Latanoprost was tested on animals.

[181] Dr. Stjernschantz, Dr. Wolff and Dr. Neufeld addressed these tests, while Dr. Flach, Dr. Leibowitz, Dr. Cullen criticized the test data.

[182] The Applicants’ experts said that the animals used and experiments performed were within the common models in the 1980s to test ophthalmological drugs. Cats were used to test for irritation, rabbits to test for hyperemia, healthy humans used to test IOP and monkeys to test for IOP effects. The POSITA would understand that normal scientific practices were used, such as using albino rabbits to measure hyperemia. The patent does not promise with absolute certainty that the compound will be effective in all patients as the Respondent’s experts allege should be the case.

[183] Dr. Flach and Dr. Cullen each criticized the type and quantity of test animals used as well as the methods of observation utilized. Both stated that utilizing cats and rabbits in ocular tests does not provide an adequate indication of toxicity in human subjects.

[184] Dr. Leibowitz stated that the inventors could not soundly predict that Latanoprost would lack side effects because the disclosure, as compared to the prostaglandin derivatives found in the '560 patent, does not show a clear and definite trend that would constitute an unexpected property.

[185] At the hearing, the Respondent alleged that the '132 Patent failed to address the gap between the single dose studies found within the patent and the fact that the treatment of glaucoma or ocular hypertension requires chronic use of medication, i.e. long-term and usually life-time treatments. None of the Respondent's experts made reference to this in their affidavits nor did they address this factor when speaking about the NOA prior art.

[186] I am satisfied that the evidence tendered by Dr. Wolff and Dr. Neufeld supports the claim for sound prediction utility.

vi) Overbreadth

[187] The Respondent argued that the '132 Patent is invalid because the claims in issue are broader than the invention claimed.

[188] The test for overbreadth is set out in *Lowell Manufacturing Co. and Maxwell Ltd. v. Beatty Bros. Ltd.* (1962), 41 C.P.R. 18 (Ex. Ct.), at 66, where the Court said that "[i]f the claims read fairly on what has been disclosed and illustrated in the specification and drawing, as they do, they are not wider than the invention…".

[189] Relying on the evidence of Dr. Maxey and Dr. Neufeld, the Applicants submit that the claims in issue are not broader than the invention disclosed. The Respondent, relying on the evidence of Dr. Leibowitz, takes the contrary view.

[190] Dr. Leibowitz said that claims do not include the use for the treatment of humans. He said Claims 19. 31, 37 and 38 are overbroad because there is no disclosure dealing with the prevalence of irritation or hyperemia.

[191] However, I prefer the evidence of the Applicants. The Respondent's arguments are based upon the fact that hyperemia was not included in the claims. It was within the discretion of the inventors of the '132 Patent to refrain from making a claim in relation to hyperemia. The claims in issue are not overbroad because the inventors decided not to claim a particular benefit.

IV. CONCLUSION

[192] In my opinion, the Respondent proceeded in this case upon a mistaken premise. It urged, from the beginning, that the '132 Patent should be construed as requiring chronic treatment. It argued that, measured against this requirement, the '132 Patent was invalid on several grounds,

including overbreadth and lack of sound prediction. The Respondent, however, was unable to show that its basic premise was sound. It follows that the arguments founded on that basic premise did not succeed.

[193] In conclusion, I am satisfied that the Applicants have demonstrated on a balance of probabilities that the allegations of invalidity set out by the Respondent in its NOA dated March 4, 2008 respecting the ‘132 Patent are not justified. It follows that the Gillette Defence is not available to the Respondent.

[194] Accordingly, the Applicants are entitled to an Order of Prohibition relative to the ‘132 Patent and an Order will issue in that regard, with costs to the Applicants.

JUDGMENT

THIS COURT ORDERS AND ADJUDGES that the application for an Order of Prohibition in respect of the 1,339,132 Patent is granted with costs to the Applicants.

"E. Heneghan"
Judge

FEDERAL COURT

SOLICITORS OF RECORD

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