Federal Court  Cour fédérale

Date: 20171025

Docket: T-1064-13

Citation: 2017 FC 951

Ottawa, Ontario, October 25, 2017

PRESENT: The Honourable Mr. Justice Manson

BETWEEN:

APOTEX INC.

Plaintiff

and

PFIZER CANADA INC.

Defendant /Plaintiff by Counterclaim

and

PHARMACIA AKTIEBOLAG

Plaintiff by Counterclaim

ORDER AND REASONS

[1] This is a motion by Apotex Inc. to further amend its Amended Reply and Defence to Counterclaim pursuant to Rule 75(1) of the *Federal Courts Rules*, SOR/98-106 [Federal Courts Rules].

I. Background

[2] Apotex Inc. is an Ontario corporation that manufactures "generic" pharmaceuticals, which are similar to drugs previously marketed under brand names.

[3] Pfizer Canada Inc. is a Canadian corporation and Pharmacia Aktiebolag is a Swedish corporation. They are subsidiaries of Pfizer Inc., which is a pharmaceutical corporation based in the United States.

[4] Pfizer holds Canadian Patent Number 1,339,132 (the "132 Patent"). The 132 Patent relates to latanoprost, which is a medicine used to treat glaucoma and ocular hypertension.

[5] Apotex alleges that on June 20, 2007, its apo-latanoprost solution, which is similar to latanoprost, became approvable under the *Food and Drug Regulations*, CRC, c 870. However, Apotex could not obtain a Notice of Compliance ("NOC") because Pfizer held the 132 Patent for latanoprost.

[6] On March 4, 2008, Pfizer received a Notice of Allegation ("NOA") from Apotex. In it, Apotex alleged that the 132 Patent was invalid on several grounds and that the apo-latanoprost solution would not infringe that patent.

[7] While Pfizer successfully defended the 132 Patent before this Court on April 26, 2010, on appeal, the Federal Court of Appeal ("FCA") on August 16, 2011, found there was no sound

prediction of the 132 Patent's promise that latanoprost could be used chronically for the treatment of glaucoma or ocular hypertension without eliciting unwanted side effects (*Apotex Inc v Pfizer Canada Inc*, 2011 FCA 236 [*Latanoprost*]).

[8] On August 19, 2011, Apotex obtained a NOC for apo-latanoprost.

[9] On June 14, 2013, Apotex filed a statement of claim seeking damages for the period of time in which apo-latanoprost was approvable but a NOC could not be obtained.

[10] In response, Pfizer filed a statement of defence and counterclaim arguing that the 132 Patent was valid, given that NOC proceedings are not determinative of infringement and validity, that Apotex would have infringed if it entered the market before the *Latanoprost* decision came out, and that Apotex had infringed ever since it brought apo-latanoprost to market.

[11] Apotex replied on the basis that the 132 Patent was invalid and/or not infringed. The invalidity allegations included, among other things: failure to pay a prescribed fee; double patenting; anticipation; lack of utility; obviousness; overly broad claims; and insufficient disclosure.

[12] On June 30, 2017, the Supreme Court of Canada ("SCC") released its decision in *AstraZeneca Canada Inc v Apotex Inc*, 2017 SCC 36 [*Esomeprazole*], which held that the "promise of the patent" doctrine ("Promise Doctrine") is unsound, insofar as it has been applied

to the question of utility of a patented invention under section 2 of the *Patent Act*, RSC 1985, c P-4 [Patent Act].

[13] The SCC held that while overpromising is a mischief, it is improper to import section 27(3) sufficiency concerns which may include overpromising issues into the section 2 utility requirement.

[14] At paragraphs 44, 46 and 51 of the *Esomeprazole* decision, the SCC states:

> **44** The Promise Doctrine effectively imports s. 27(3) into s. 2 inappropriately, by requiring that to satisfy the utility requirement in s. 2, any disclosed use (by virtue of s. 27(3)) be demonstrated or soundly predicted at the time of filing. If that is not done successfully, the entire patent is invalid, as the pre-condition for patentability – an invention under s. 2 of the Act – has not been fulfilled.
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> **46** The scheme of the Act treats the mischief of overpromising in multiple ways. There are consequences for failing to properly disclose an invention by claiming, for instance, that you have invented more than you have. A disclosure which is not correct and full, or states an unsubstantiated use or operation of the invention, may be found to fail to fulfill the requirements of s. 27(3). An overly broad claim may be declared invalid; however, under the operation of s. 58 of the *Patent Act*, remaining valid claims can be given effect. As well, this mischief may result in a patent being void under s. 53 of the Act, where overpromising in a specification amounts to an omission or addition that is "willfully made for the purpose of misleading".
>
> **51** The effect of the Promise Doctrine to deprive such an invention of patent protection if even one "promised" use is not soundly predicted or demonstrated is punitive and has no basis in the Act. Furthermore, such a consequence is antagonistic to the bargain on which patent law is based wherein we ask inventors to give fulsome disclosure in exchange for a limited monopoly (*British United Shoe Machinery Co. v. A. Fussell & Sons Ltd.* (1908), 25 R.P.C. 631(C.A.), at p. 650). To invalidate a patent solely on the basis of an unintentional overstatement of even a single use will discourage a patentee from disclosing fully, whereas such

> disclosure is to the advantage of the public. The Promise Doctrine in its operation is inconsistent with the purpose of s. 27(3) of the Act which calls on an inventor to "fully describe the invention and its operation or use". Thus, the Promise Doctrine undermines a key part of the scheme of the Act; it is not good law.

[15] On July 5, 2017, Apotex advised Pfizer of its intention to amend its pleadings due to the change in law caused by *Esomeprazole*. Pfizer requested the amendments as soon as possible, given that expert reports were due in three weeks. Pfizer also expressed concerns with the potential loss of the scheduled trial dates beginning in January 2018.

[16] On July 18, 2017, Apotex provided Pfizer with its proposed amendments, which were extensive.

[17] On July 19, 2017, at a Case Management Conference (“CMC”), the Court suspended the deadline for expert reports.

[18] On July 25, 2017, Pfizer advised Apotex that they opposed the majority of the amendments and provided reasons for their position.

[19] On July 26, 2017, at a CMC, the trial date was vacated and a new trial date has been scheduled to commence on November 5, 2018.

[20] On September 22, 2017, Apotex submitted its revised amendments. While Pfizer does not object to most of the proposed amendments, Pfizer takes issue with three of Apotex's proposed new pleas:

i. In paragraph 10B, Apotex alleges that in the but-for world from 2007 to 2011, the Court would have invalidated Pfizer's patent using the "Promise Doctrine", which was the applicable law at that time, not the current law as recently determined by the SCC in the *Esomeprazole* decision. Pfizer takes the position that Apotex is alleging that it would have been able to invalidate Pfizer's patent using an unsound legal doctrine, which is a vexatious and ultimately an absurd plea (the "hypothetical invalidity plea");

Pfizer states that in paragraphs 136A and 145A and 145B, Apotex essentially re-argues the Promise Doctrine, asserting the patent "over promises" because the inventors had not demonstrated or soundly predicted the utility rendering the disclosure and claims invalid for:

ii. Insufficiency; and
iii. Overbreadth.

Pfizer argues that with these amendments, Apotex is improperly trying to repackage the arguments related to the Promise Doctrine rejected by the SCC in *Esomeprazole*.

[21] Pfizer seeks all costs arising from the amendments and opposes the above three proposed amendments (the "Impugned Amendments").

II. Issues

[22] The issues are:

A. Do the claims disclosed in the Impugned Amendments disclose reasonable defences?;

B. Would these amendments result in an injustice to Pfizer that is not capable of being compensated by costs and would the interests of justice be served by allowing the amendments?; and

C. Should Pfizer be awarded their costs arising from Apotex's amendments?

III. Analysis

A. *Do the claims disclosed in the Impugned Amendments disclose reasonable defences?*

[23] The parties generally agree on the law governing motions to amend pleadings. Rule 75 of the Federal Courts Rules provides that the Court may allow a party to amend a pleading "at any time…on such terms as will protect the rights of the parties".

[24] Firstly, the Court should be satisfied that it is in the interests of justice to do so. In considering whether the interests of justice would be served by permitting amendments, the Court may consider a number of factors, including:

a) The timelines of the motion to amend;
b) The extent to which the proposed amendments would delay the expeditious trial of the matter;
c) The extent to which a position taken originally by one party has led another party to follow a course of action in the litigation which it would be difficult or impossible to alter; and
d) Whether the amendments sought will facilitate the Court's consideration of the true substance of the dispute on its merits.

(*Abbvie Corp v Janssen Inc*, 2014 FCA 242 at para 3, referring to *Continental Bank Leasing Corp v R*, [1993] TCJ No 18 (QL)).

[25] Moreover, the Court should be satisfied that permitting amendments will not cause an injustice that cannot be compensated by an award of costs. As stated in *Canderel Ltd v Canada*, [1994] 1 FC 3 (CA) at 10 (cited with approval in *Merck & Co Inc v Apotex Inc*, 2003 FCA 488 [*Lisinopril*] at paras 30 and 64):

> . . . while it is impossible to enumerate all the factors that a judge must take into consideration in determining whether it is just, in a given case, to authorize an amendment, the general rule is that an amendment should be allowed at any stage of an action for the

> purpose of determining the real questions in controversy between the parties, provided, notably, that the allowance would not result in an injustice to the other party not capable of being compensated by an award of costs and that it would serve the interests of justice.

[26] Finally, the absence of a reasonable prospect of success is a well-established reason for the Court to dismiss a motion for leave to amend (*Teva Canada Limited v Gilead Sciences Inc*, 2016 FCA 176 [*Gilead*] at para 29). Only if the amendment has a reasonable prospect of success will the Court investigate other matters, such as prejudice the opposing party may suffer as a result of the amendment (*Gilead* at para 31).

[27] In deciding whether a pleading stands a reasonable prospect of success, the Court must accept the alleged facts as proven and only find it unreasonable where it is plain and obvious or beyond reasonable doubt that the pleading cannot succeed (*Lisinopril* at para 43). The burden is on the amending party to demonstrate such a reasonable prospect of success (*Lisinopril* at para 46).

[28] Pfizer's submission is that none of the Impugned Amendments have a reasonable prospect of success.

i. Hypothetical Invalidity

[29] Apotex's proposed amendment reads as follows:

> **[10B]** Had Pfizer commenced a hypothetical patent infringement action in the but-for world in response to Apotex's market entry with Apo-latanoprost on June 20, 2007, which is expressly denied, the trial of that patent infringement action, the trial decision in that patent infringement action and the decisions on any appeals

> therefrom would have been completed or rendered before August 16, 2011, and, in the alternative, long before the release of the Supreme Court of Canada's decision in *AstraZeneca v Apotex*, 2017 SCC 36, such that the "promise doctrine" described in that decision would have been applied by the Court(s) in that hypothetical patent infringement action to invalidate the 132 Patent. The Court(s) would have arrived at the same conclusion in that hypothetical patent infringement action that the Federal Court of Appeal arrived at in Federal Court File No. A-206-10 (2011 FCA 236), namely, that the promise of the 132 Patent is to treat glaucoma and intraocular hypertension on a chronic basis without causing substantial side effects, and that there was no demonstration or sound prediction of that promised utility by the filing date, rendering the 132 Patent invalid for lack of utility. In the but-for world, Apotex thus would not have been held to infringe the 132 Patent had it commenced marketing and selling Apo-Latanoprost on June 20, 2007 or at any time prior to the grant of its NOC.
>
> [Emphasis mine]

[30] Accordingly, it is Apotex's position that if Pfizer commenced a patent infringement action in response to Apotex's market entry in 2007, prior to *Esomeprazole*, the Promise Doctrine would have been applied to invalidate the 132 Patent.

[31] In response, Pfizer argues that the Court is in no position to knowingly apply incorrect legal principles to adjudicate what would have happened. The issue is whether the 132 Patent is valid; the fact it might have been invalidated under different law is irrelevant.

[32] In a claim for damages under section 8 of the *Patented Medicines (Notice of Compliance) Regulations*, SOR/93-133, the Court's task is to assess a hypothetical world where the impugned

conduct did not take place (*Pfizer Canada Inc v Teva Canada Limited*, 2016 FCA 161 [*Venlafaxine*] at para 46). As the Court stated in *Venlafaxine* at paragraph 50:

> Both "would have" and "could have" are key. Compensatory damages are to place plaintiffs in the position they would have been in had a wrong not been committed. Proof of that first requires demonstration that nothing made it impossible for them to be in that position—i.e., they could have been in that position. And proof that plaintiffs would have been in a particular position also requires demonstration that events would transpire in such a way as to put them in that position—i.e., they would have been in that position.

[33] Neither party referred to any case law that would really help determine whether the outcome of a hypothetical infringement action in the past might have been different than in the present, due to an intervening change in law – here, that change being the SCC decision in *Esomeprazole*.

[34] Apotex argues that the Court should not reach "back to the future" in considering whether current case law would have influenced or determined the outcome in the hypothetical but-for world ten years ago, when the law as it was then developed, relating to utility and promise of the patent, was good law and would have been applied in a different context than today.

[35] Pfizer counters that it would be absurd to do other than apply the law as it now is and should have been at the earlier date, given the recent decision of the SCC in *Esomeprazole* and the fact that validity attacks based on inutility have been wrongly applied by the Courts over the relevant period.

[36] Notwithstanding it may be a difficult argument for Apotex at trial, this is not a straight-forward question of law to determine on a motion to amend. The Court should have a fulsome record before it, in order to decide what is no doubt an important legal question, with lasting and long-reaching implications for the parties and for others who face the same question. It should be left for consideration by the trial judge, after final argument in the context of the relevant facts and law (*Mercks et al v Apotex et al*, 2012 FC 454 at paras 30-31, citing *Hunt v Carey Canada Inc*, [1990] 1 SCR 959 at 980; *Fullowka v Whitford*, 1996 CanLII 10199 (NWT CA) at para 22; and *R v Imperial Tobacco*, 2011 SCC 42 at para 21).

[37] The amended paragraph 10(B) is allowed.

ii. Insufficiency

[38] Apotex's proposed amendments read as follows:

> **[145A]** Because the 132 Patent overpromises, it contains a disclosure that is not correct and full and it states an unsubstantiated use or operation of the purported invention, which constitutes a failure to fulfill the requirements of subsection 27(3) of the *Patent Act* (and/or section 36 of the *Patent Act* as it existed before 1989), thereby rendering the 132 Patent and all of the Asserted Claims invalid.
>
> **[145B]** As described above, the 132 Patent asserts that latanoprost can be usefully administered on a chronic basis for the treatment of glaucoma or ocular hypertension without causing substantial side effects. However, for the reasons described under the headings "Lack of Utility" and "No Demonstrated Utility/ Lack of Sound Prediction", there was no demonstration or sound prediction of this before the filing date of the 132 Patent and this was never in fact achieved. The 132 Patent thus asserts an unsubstantiated use or operation for the invention, which constitutes the mischief of overpromising and renders all of the Asserted Claims invalid for

> failure to fulfill the requirements of subsection 27(3) of the *Patent Act* (and/or section 36 of the *Patent Act* as it existed before 1989).
>
> [Emphasis added]

[39] Section 27(3) of the Patent Act states that the specification must:

a. Correctly & fully describe the invention & its operation or use as contemplated by the inventor;
b. Set out clearly the various steps in a process, or the method of constructing, making, compounding or using a machine, manufacture or composition of matter, in such full, clear and concise terms as to enable any person skilled in the art or science to which it pertains, or with which it is most closely connected, to make, construct, composed or use it;

[40] Apotex's position is that because the 132 Patent overpromises, it contains a disclosure that is not correct and full and states an unsubstantiated use or operation of the invention, which constitutes a failure to fulfill the disclosure requirements of section 27(3) of the Patent Act.

[41] Pfizer argues that Apotex is improperly trying to insert the Promise Doctrine into the sufficiency of disclosure analysis, which was rejected in *Esomeprazole*. Courts have consistently maintained the distinction between the disclosure requirement under section 27 of the Patent Act and the utility requirement under section 2 of the Patent Act. There can be no conflation of these two legal concepts.

[42] Justice Brown recently decided in *Pfizer Canada Inc v Apotex Inc*, 2017 FC 774 [*Pfizer*] that not only was the Promise Doctrine not good law in terms of utility but also overbreadth of claims and insufficiency of patent specifications, as the SCC did not specifically endorse the Promise Doctrine with respect to construing section 27(3) of the Patent Act and would have done so if that was the Court's intention.

[43] In *Pfizer*, Justice Brown held at paragraphs 359, 360, 363 and 365:

> **359** While I do not fault Apotex for raising its "overpromise" doctrine given the invitation to make additional comments on *AstraZeneca*, I note Apotex did not ask to raise "overpromising" in its letter of July 4, 2017, in which it requested a broadening of the scope of post hearing submissions: it only asked to raise anticipation and obviousness. Thus, while Apotex raised obviousness in its post-hearing filings, it said nothing about anticipation; instead it raised the new issue of "overpromising".
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> **360** I also observe that the alleged overpromises resemble the promise arguments advanced by Apotex, which are no longer valid having regard to *AstraZeneca*. If the Supreme Court intended to say, in effect, that the Promise Doctrine was not good law in terms of utility under s 2, but was good law in terms of patent specifications under subsection 27(3) it could have done so; it did not.
>
> **363** …I am unable to see a rationale for the argument that the Supreme Court of Canada removed the Promise Doctrine from the utility analysis yet simultaneously required it to be considered, in the manner Apotex proposes, in the specification analysis. If that was the case, a major underlying problem identified by the Supreme Court itself would remain, namely that "a patentee will be dissuaded from stating the invention can be used for things that are not sufficiently established at the time of filing if doing so would risk invalidating the entire patent." See *AstraZeneca* para 45.
>
> **365** I see nothing in *AstraZeneca* that alters what I take from the foregoing namely that the specifications analysis under subsection 27(3) requires the patentee to define the precise and exact extent of the exclusive property and privilege claimed. In addition, nothing in *AstraZeneca* departs from the proposition that under subsection 27(3), "the applicant must disclose everything that is essential for the invention to function properly. To be complete, it must meet two conditions: it must describe the invention and define the way it is produced or built ... The applicant must define the nature of the invention and describe how it is put into operation. A failure to meet the first condition would invalidate the application for ambiguity, while a failure to meet the second invalidates it for insufficiency." See *Teva* at para 51 citing to *Pioneer Hi-Bred Ltd v Canada (Commissioner of Patents)*, [1989] 1 SCR 1623, pp. 1637-38.

[44] Apotex argues that to the extent the *Pfizer* decision stands for the proposition that the SCC removed overpromising as a basis for finding insufficiency or overbreadth because it did not clearly state it was a valid argument on those issues, the *Pfizer* decision overstates the effective result of the SCC *Esomeprazole* decision.

[45] What is apparent is that the SCC did not equate the application of the Promise Doctrine to utility with the potential for overpromising to be a relevant factor in determining validity with respect to insufficient disclosure under section 27(3) or due to claim overbreadth.

[46] Apotex states that this is particularly true when one reasonably considers that the SCC stated in *Esomeprazole*, at paragraph 46:

> The scheme of the Act treats the mischief of overpromising in multiple ways. There are consequences for failing to properly disclose an invention by claiming, for instance, that you have invented more than you have. A disclosure which is not correct and full, or states an unsubstantiated use or operation of the invention, may be found to fail to fulfill the requirements of s. 27(3). An overly broad claim may be declared invalid; however, under the operation of s. 58 of the *Patent Act*, remaining valid claims can be given effect. As well, this mischief may result in a patent being void under s. 53 of the Act, where overpromising in a specification amounts to an omission or addition that is "willfully made for the purpose of misleading".

[47] Apotex also argues that there is nothing in the SCC *Esomeprazole* decision that precludes making an “overpromising” argument for insufficiency or overbreadth of claims, as an unsubstantiated use or operation of the purported invention, even if it amounts to a “repackaging” of the inutility attack under a different legal guise. It is a separate ground of attack, and a sufficiently important legal question not to be struck on a motion to amend, but

should be left for the trial judge to decide on a full legal and factual foundation. It is, Apotex argues, not an amendment that has no reasonable prospect for success.

[48] However, the impugned insufficiency amendment in the Apotex pleading relies solely on the same factual basis as the inutility plea held invalid by the SCC in *Esomeprazole* and as relied upon in the earlier Apotex pleading. It does not address, on a different factual basis, the question of whether the disclosure enabled a person of ordinary skill in the science or field of the invention to produce it, using only the instructions contained in the specification (*Pioneer Hi-Bred Ltd v Canada (Commissioner of Patents)*, [1989] 1 SCR 1623 at 1628).

[49] As stated by the SCC in *Teva Canada Ltd v Pfizer Canada Inc*, 2012 SCC 60 at excerpts from paragraphs 49-52:

> **49** In *Consolboard*, this Court reviewed the Act's disclosure requirements, which at that time were found in s. 36. Although there are variations in wording between that section and the current s. 27(3), the substance of the disclosure requirements has remained the same.
>
> **50** Dickson J. discussed what the specification must contain in order to meet the disclosure requirements. He stated clearly that the nature of the invention must be disclosed and that the entire specification, including the claims, must be considered in determining the nature of the invention and whether disclosure was sufficient:
>
> > […]
> >
> > Section 36(1) (now section 27) seeks an answer to the questions: "What is your invention? How does it work?" With respect to each question the description must be correct and full in order that, as Thorson P. said in *Minerals Separation North American Corporation v. Noranda Mines, Limited* [1947] Ex. C.R. 306]:

> ... when the period of monopoly has expired the public will be able, having only the specification, to make the same successful use of the invention as the inventor could at the time of his application. [at p. 316]
>
> Since *Consolboard*, the Court has constantly applied the principles stated by Dickson J., which is a testament to the soundness of his reasoning: see, e.g., *Monsanto Canada Inc. v. Schmeiser*, 2004 SCC 34, [2004] 1 S.C.R. 902, at para. 18; *Whirlpool Corp. v. Camco Inc.*, 2000 SCC 67, [2000] 2 S.C.R. 1067, at para. 52; *Pioneer Hi-Bred Ltd. v. Canada (Commissioner of Patents)*, [1989] 1 S.C.R. 1623 ("*Pioneer Hi-Bred*"), at p. 1636.
>
> **52** In *Consolboard* and in *Pioneer Hi-Bred*, the Court correctly analysed the disclosure requirements set out in s. 27(3) of the Act. The reasoning in those cases should be reaffirmed and applied in the case at bar.

[50] I agree with Justice Pelletier of the FCA, in *Bristol-Myers Squibb Canada Co et al v Teva Canada Limited et al*, 2017 FCA 76 at paragraph 68, that "… the Supreme Court does not change substantive law by implication, particularly when it has shown a cautious approach to change in the same context: see *Apotex Inc v Eli Lilly Canada Inc*, 2016 FCA 267 at para 37".

[51] This approach resonates when one considers the history and purposive interpretation of section 27(3) of the Patent Act.

[52] In this case, the impugned insufficiency plea does not stand a reasonable prospect of success. There is no allegation that Pfizer failed to sufficiently disclose what the invention is or how the invention can be used. Nothing has changed the applicable test for sufficiency of a disclosure and Apotex's impugned plea must fail.

[53] The impugned insufficiency amendment is not allowed.

iii. Overbreadth

[54] Apotex's proposed amendment reads as follows:

> **[136A]** As described above, the 132 Patent asserts that latanoprost can be chronically administered for the treatment of glaucoma or ocular hypertension without causing substantial ocular irritation. However, for the reasons described under the headings "Lack of Utility" and "No Demonstrated Utility / Lack of Sound Prediction", there was no demonstration or sound prediction of this before the filing date of the132 Patent and this was never achieved. This constitutes the mischief of overpromising and renders all of the Asserted Claims invalid for overbreadth:
>
> (a) claim 12 (which claims a therapeutic ophthalmological composition containing latanoprost for the treatment of glaucoma or ocular hypertension in an amount sufficient to reduce intraocular pressure without causing substantial ocular irritation) is invalid for overbreadth because glaucoma and ocular hypertension are chronic disorders that require chronic administration of a medicament for treatment and this is more than what the named inventors of the 132 Patent had invented because they had not demonstrated or soundly predicted that the subject matter of claim 12 would not cause substantial ocular irritation upon the chronic administration required for the treatment of glaucoma or ocular hypertension. The 132 Patent improperly asserts that the claimed composition can be usefully administered on a chronic basis for the treatment of glaucoma or ocular hypertension without causing substantial side effects;
>
> (b) claim 19 (which claims latanoprost) is invalid for overbreadth because the 132 Patent asserts that latanoprost can be usefully administered on a chronic basis for the treatment of glaucoma or ocular hypertension without causing substantial side effects and this is more than what the named inventors of the 132 Patent had invented because they had not demonstrated or soundly predicted that latanoprost would not cause substantial ocular irritation and/or conjunctival hyperemia upon the chronic administration required for the treatment of glaucoma or ocular hypertension. A compound that has not been demonstrated or soundly predicted to avoid these substantial side effects upon chronic administration cannot be useful in the treatment of glaucoma or ocular hypertension.

> Further, while the 132 Patent asserts that its invention is limited in scope to compounds that can be usefully administered on a chronic basis for the treatment of glaucoma or ocular hypertension without causing substantial side effects, claim 19 claims a compound without limitation as to its properties and thus is necessarily overly broad relative to the invention made or disclosed;
>
> (c) claim 31 (which claims the use of latanoprost in the treatment of glaucoma or ocular hypertension) is invalid for overbreadth because glaucoma and ocular hypertension are chronic disorders that require chronic administration of medicament for treatment and this is more than what the named inventors of the 132 Patent had invented because they had not demonstrated or soundly predicted that latanoprost would be useful upon the chronic administration required for the treatment of glaucoma or ocular hypertension. Further, a compound that has not been demonstrated or soundly predicted to avoid substantial side effects upon chronic administration cannot be useful in the treatment of glaucoma or ocular hypertension. The 132 Patent improperly asserts that latanoprost can be usefully administered on a chronic basis for the treatment of glaucoma or ocular hypertension without causing substantial side effects;
>
> (d) claim 38 (which claims the use of latanoprost in the treatment of glaucoma or ocular hypertension) is invalid for overbreadth for the same reasons as claim 31.
>
> [Emphasis added]

[55] Apotex thereby alleges that several claims in the 132 Patent assert that latanoprost can be chronically administered without causing substantial ocular irritation, but there has been no demonstration or sound prediction of this advantage. This constitutes the mischief of overpromising referred to by the SCC in *Esomeprazole* and renders the claims invalid for overbreadth.

[56] Pfizer argues that this is again an attempt to circumvent the reasoning of the SCC in *Esomeprazole* and improperly conflates overbreadth with utility, which is what Apotex has done

with the impugned pleas related to insufficiency under section 27(3). Assertions that rely on utility as the basis for overbreadth are incorrect in law.

[57] As the FCA has consistently held, a claim is overly broad and invalid if it asserts an exclusive property or privilege in something the inventor did not actually invent or did not fully disclose (see, for example, *Pfizer Canada Inc v Canada (Health)*, 2007 FCA 209 at para 116).

[58] Apotex's allegation of overbreadth stands a reasonable prospect of success. The claims in the 132 Patent repeatedly refer to latanoprost with respect to the "treatment of glaucoma or ocular hypertension...without causing substantial ocular irritation" and "use …in the treatment of glaucoma or ocular hypertension." Apotex alleges that latanoprost cannot be used chronically without causing substantial irritation and therefore cannot be used in the treatment of glaucoma and ocular hypertension. To the extent that a claimed use is unsubstantiated, an allegation of an overly broad claim may succeed.

[59] While the onus is on Apotex to prove this invalidity plea at trial, and it may be difficult to do so, it has a reasonable prospect of success. The amendment is allowed.

B. *Would these amendments result in an injustice to Pfizer that is not capable of being compensated by costs and would the interests of justice be served by allowing the amendments?*

[60] Having decided the issues above relating to the Impugned Amendments, I find that the amendments, as allowed, will not result in an injustice not capable of being compensated by costs and that it is in the interests of justice to allow the amendments.

[61] As pointed out by Apotex, non-compensable prejudice does not include prejudice resulting from potential success of the proposed plea or the fact that the amended plea may increase the length or complexity of the trial. The parties have agreed to the trial being adjourned until November 2018, so timing is no longer an issue.

[62] As well, given the recent decision of the SCC in *Esomeprazole* has materially changed the law, and given that the Impugned Amendments as allowed are related to that decision, this Court should permit the amendments.

[63] Moreover, in the absence of any asserted prejudice to Pfizer flowing from the purported "lateness" of the proposed amendments, "lateness" alone is not a sufficient ground to deny the amendments.

C. *Should Pfizer be awarded their costs arising from Apotex's amendments?*

[64] Pfizer seeks all costs arising from Apotex's amendments such as amending pleadings, reviewing its strategy and document production, and additional discovery and use of experts.

[65] The change in law caused by *Esomeprazole* required pleading amendments to facilitate the Court's consideration of the issues in the dispute on their merits.

[66] However, there were delays and costs associated with the amendments. The initial amendments were extensive and added several pages to the pleadings. Moreover, it was only in response to Pfizer's prior objections that Apotex eventually provided amendments in a form

substantially agreed to by Pfizer, excepting the Impugned Amendments. In the meantime, the trial date was vacated. It is unclear to what extent additional discovery and use of experts maybe required, or what costs are properly attributable to the amended pleadings being now relied upon by Apotex. It is also questionable whether some or many of the amendments truly result from the SCC *Esomeprazole* decision, or could not have been made much earlier.

[67] Apotex shall bear the costs of the motion and the Court will consider possible additional costs attributable to the amendments with respect to additional discovery and use of experts after final submissions at trial.

ORDER in T-1064-13

THIS COURT ORDERS that:

1. Apotex's motion to further amend its Amended Reply and Defence to Counterclaim in the form attached as Schedule A hereto is allowed, except for paragraph 10B, which is hereby struck;

2. Pfizer shall have 30 days from the date of this Order to serve and file a Further Amended Reply to Defence to Counterclaim;

3. Costs to Pfizer in any event, to be determined by the trial judge following final submissions at trial.

"Michael D. Manson"
Judge

SCHEDULE A

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Court File No. T-1064-13

FEDERAL COURT

BETWEEN:

APOTEX INC.

Plaintiff
(Defendant by Counterclaim)

- and -

PFIZER CANADA INC.

Defendant
(Plaintiff by Counterclaim)

- and -

PHARMACIA AKTIEBOLAG

Plaintiff by Counterclaim

FURTHER AMENDED REPLY AND DEFENCE TO COUNTERCLAIM
(dated September 15, 2017)

1. By way of reply, save and except as may be hereinafter expressly admitted and save and except as to admissions, the Plaintiff and Defendant by Counterclaim, Apotex Inc. ("Apotex"), denies each and every allegation set out in the Further Amended Statement of Defence and Counterclaim dated ^ April 4, 2014 (the "Defence") and puts the Defendant to the strict proof thereof.

2. Apotex further repeats and relies upon the allegations set forth in its Statement of Claim (the "Claim").

I. The Apotex Claim (paras. 11 to 14 of the Defence)

3. Apotex denies the allegations made in paragraphs 11 through 14 of the Defence and further states that it has properly pleaded all facts relevant to a claim for damages made pursuant to section 8 of the *Patent Regulations*, as that term is defined in the Claim, which is intended to redress a claimant's inability to come to market at a particular time, namely, the date upon which, in the absence of the *Patent Regulations*, the Minister would have issued an NOC. Accordingly, Apotex denies that the Claim fails to particularize the necessary facts relevant to the Claim. Indeed, the alleged particulars sought are not material facts but, to the extent relevant, constitute advanced discovery disclosure of evidentiary issues which will be addressed during the course of the proceeding and at trial.

II. Assessment of Damages (paras. 15 to 20 of the Defence)

4. With respect to paragraphs 15, 16 and 18 of the Defence, Apotex states that these allegations fail to plead any facts, material or otherwise, relevant to the issues in dispute. Issues of burden and assertions as to the evidence which must be lead at trial are not matters of fact, but are argument. Accordingly, these paragraphs are irrelevant, embarrassing and frivolous and ought to be struck.

5. With respect to paragraph 17 of the Defence, Apotex again states that same fails to plead any fact, material or otherwise, relevant to the issues in dispute. Setting out a laundry list of the documents which may be sought by way of disclosure is not a matter of fact, but again of argument or, at best, advanced discovery disclosure of evidentiary issues. Accordingly, paragraph 17 of the Defence is irrelevant, embarrassing and frivolous and ought to be struck.

6. With respect to subparagraph 18(c) and paragraph 19 of the Defence, Apotex denies that the principle of mitigation has any application to the circumstances at bar. In the alternative, to the extent that the Defendant's allegations in respect of mitigation are in any way relevant, Apotex pleads that it acted reasonably throughout.

7. With respect to paragraph 19 of the Defence and the Defendant's assertion that Apotex is only entitled to a reduced period of liability due to a purported delay in Apotex sending its notice of allegation ("NOA"), Apotex states that such allegation stems from a fundamental misinterpretation of the terms of the *Patent Regulations* and their application to the losses suffered by Apotex.

8. The liability period under section 8 of the *Patent Regulations* is the period commencing upon the date that the Minister was to have issued the NOC in the absence of the *Patent Regulations*. There is no obligation under the *Patent Regulations* to serve an NOA at any particular time, nor is any such perceived "obligation" referable to any period of liability under the *Patent Regulations*. Accordingly, Apotex states that the Defendant's allegations insofar as Apotex's NOA are concerned fail to raise a cognizable defence. Accordingly, Apotex denies the

allegation made at paragraph 19 of the Defence that "a more appropriate date" for the commencement of the damage period is March 6, 2008.

III. Infringement irrelevant (paras. 21 to 35 of the Defence)

9. In paragraphs 21 to 35 of the Defence, and in the Counterclaim, the Defendant pleads a series of irrelevant and groundless allegations. More particularly:

(a) The Defendant is precluded from alleging hypothetical infringement during the period asserted in the Claim as same seeks to reverse the decision of the Court in Federal Court File No. A-206-10, and is therefore an improper collateral attack thereupon and is otherwise an abuse of the Court's process. The Defendant is estopped from so doing;

(b) To permit a defendant to defend a claim for compensation as a consequence of the wrongful invocation of the *Patent Regulations* by asserting hypothetical infringement would undermine the intent of the *Patent Regulations* and would provide an unmitigated incentive to patentees and their privies to prosecute a proceeding under the *Patent Regulations* in every instance since there would be absolutely no consequence to the wrongful prosecution of such a proceeding;

(c) Without admitting that Apotex infringes Canadian Letters Patent No. 1,339,132 (the "132 Patent"), which it does not, any question of infringement is irrelevant to a claim pursued by a second person such as Apotex consequent upon the

dismissal or withdrawal of a prohibition application brought under the *Patent Regulations*;

(d) As outlined above, the relevant query for any section 8 analysis is as to events which would have taken place upon market entry at the time of approvability (in this case, June 2007). Accordingly, any question of infringement in respect of the product currently being marketed and sold is irrelevant; and

(e) Subsection 8(3) of the *Patent Regulations* expressly provides that the Court may make an order under section 8 "without regard to whether the first person has commenced an action for the infringement of a patent that is the subject matter of the application".

10. In any event, for the reasons set forth in the Defence to Counterclaim below, Apotex denies the allegations made in paragraphs 21 to 35 of the Defence that it would have infringed the 132 Patent had it commenced marketing and sale of its Apo-Latanoprost solution on June 20, 2007 or at any time prior to the grant of its NOC.

10A. Apotex denies that Pfizer could have and/or would have commenced a hypothetical patent infringement action against Apotex relating to Apo-latanoprost in the but-for world and puts Pfizer to the strict proof thereof. In the real world, when Apotex launched Apo-latanoprost in 2011, Pfizer did not commence a patent infringement action against Apotex and Pfizer has never commenced a patent infringement action against Apotex relating to Apo-latanoprost. In the real world, Pfizer merely counterclaimed for patent infringement against

Apotex in response to Apotex's section 8 claim in 2013. In the real world, in the absence of the section 8 claim commenced by Apotex, Pfizer never could have and/or would have commenced a patent infringement action against Apotex relating to Apo-latanoprost. In the but-for world, Apotex could not have and/or would not have commenced a section 8 action and Pfizer never could have and/or would have commenced a patent infringement action against Apotex relating to Apo-latanoprost.

10B. Had Pfizer commenced a hypothetical patent infringement action in the but-for world in response to Apotex's market entry with Apo-latanoprost on June 20, 2007, which is expressly denied, the trial of that patent infringement action, the trial decision in that patent infringement action and the decisions on any appeals therefrom would have been completed or rendered before August 16, 2011, and, in the alternative, long before the release of the Supreme Court of Canada's decision in *AstraZeneca v. Apotex*, 2017 SCC 36, such that the "promise doctrine" described in that decision would have been applied by the Court(s) in that hypothetical patent infringement action to invalidate the 132 Patent. The Court(s) would have arrived at the same conclusion in that hypothetical patent infringement action that the Federal Court of Appeal arrived at in Federal Court File No. A-206-10 (2011 FCA 236), namely, that the promise of the 132 Patent is to treat glaucoma and intraocular hypertension on a chronic basis without causing substantial side effects, and that there was no demonstration or sound prediction of that promised utility by the filing date, rendering the 132 Patent invalid for lack of utility. In the but-for world, Apotex thus would not have been held to infringe the 132 Patent

had it commenced marketing and selling Apo-Latanoprost on June 20, 2007 or at any time prior to the grant of its NOC.

DEFENCE TO COUNTERCLAIM

11. Apotex repeats and adopts the allegations set out in its Reply and in its Claim, and denies that Pfizer Canada or Pharmacia Aktiebolag is entitled to any of the relief sought in the Counterclaim.

12. Save and except as hereinafter may be admitted, Apotex denies each and every allegation contained in the Counterclaim.

I. Pharmacia Aktiebolag ("Pharmacia") has No Standing and is not a proper Party

13. Apotex pleads that Pharmacia is not a proper party to the Counterclaim and has no standing.

14. Apotex further states that there is no provision in the *Federal Courts Rules* for adding a party as a plaintiff to a counterclaim where that party is not a defendant to the claim. A party may only be made a defendant to a counterclaim. Accordingly, Apotex states that the claim by Pharmacia is nugatory and of no force and effect. Apotex reserves its right to move to strike same.

14A. Apotex further denies the allegations contained in paragraph 23 and 38 of the Further Amended Statement of Defence and Counterclaim to the effect that Pfizer Health AB has acquired rights in and to the 132 Patent. As of March 13, 2014, neither the 132 Patent nor the documents on file with the Canadian Patent Office reflected the acquisition of any such rights.

II. Pfizer Canada Inc. ("Pfizer Canada") has No Standing

15. Contrary to what is alleged at paragraphs 23, 39 and 40 of the Further Amended Statement of Defence and Counterclaim ^, Apotex states that Pfizer Canada has not been licensed or otherwise received any rights in respect of the 132 Patent (either with respect to Xalatan Solution, Xalacom Solution or otherwise) which would allow it to assert the within claim for infringement, and denies that Pfizer Canada has standing as a person claiming under the patentee within the meaning of subsection 55(1) of the *Patent Act* to make such a claim. More particularly, Pfizer Canada has not suffered nor will it suffer any damage that is independent of any alleged damage that could have been suffered by the patentee in respect of any act of infringement within the jurisdiction of this Honourable Court.

III. No Entitlement to the Relief Sought

16. Apotex denies that Pfizer Canada or Pharmacia are entitled to any of the relief sought in paragraph 36 of the Counterclaim and puts both to the strict proof thereof. In particular, Apotex denies that it has infringed any of the claims of the 132 Patent, including specifically the claims asserted in the Counterclaim, namely, 12, 19, 31, 37 and 38 (collectively, the "Asserted Claims"), and Apotex asserts that the Asserted Claims and the 132 Patent as a whole are and always have been invalid, void and of no force and effect for the reasons set out below.

17. With respect to paragraphs ^ 42 and 43 of the Counterclaim, Apotex admits that it received a Notice of Compliance for its Apo-Latanoprost solution on August 19, 2011 and a Notice of Compliance for its Apo-Latanoprost-Timop Solution on October 23, 2010.

18. With respect to paragraph ^ 44, 45 and 46 of the Counterclaim, Apotex admits only that it has offered for sale and sold its Apo-Latanoprost solution in Canada, and that its Apo-Latanoprost solution and its Apo-Latanoprost-Timop Solution^ contain latanoprost, but denies the remainder of the allegations therein.

19. Apotex denies the remainder of the allegations in paragraphs ^47 to 51 of the Counterclaim. The 132 Patent and each of the claims of the 132 Patent are invalid, void and of no force or effect and thus cannot be infringed by Apotex. Apotex denies that it is prohibited from alleging non-infringement of the 132 Patent as is alleged in paragraph 31 of the Defence.

19A. On May 4, 2017, Pfizer advised Apotex that it intends to elect an accounting of Apotex's profits as the only remedy in respect of the alleged infringement. On June 7, 2017, Apotex advised Pfizer that it continues to deny that Pfizer has the right to elect an accounting of Apotex's profits.

19B. In any event, in the event that there is a finding of infringement in respect of Apo-latanoprost and/or Apo-latanoprost-timolol sold (to any jurisdiction) *after* the expiration of the 132 Patent, which is expressly denied, in respect of an accounting of Apotex's profits, no (or reduced) profits are attributable to the alleged infringement and/or the use of the purported invention of the 132 Patent after said patent expired on July 29, 2014 because, in the absence

of the alleged infringement, Apotex could have and would have acquired the latanoprost active pharmaceutical ingredient ("API") from Chirogate International Inc. after the expiration of the 132 Patent, manufactured Apo-latanoprost and/or Apo-latanoprost-timolol after the expiration of the 132 Patent using this post-expiry API and sold non-infringing Apo-latanoprost and/or Apo-latanoprost-timolol (to any jurisdiction) after the expiration of the 132 Patent.

19C. Consequently, in the absence of the alleged infringement and/or in the absence of the alleged use of the purported invention of the 132 Patent, Apotex could have and would have earned substantial profits from the sale of non-infringing Apo-latanoprost and Apo-latanoprost-timolol after the expiration of the 132 Patent such that none (or not all) of the profits that Apotex actually earned on the sale of the allegedly infringing Apo-latanoprost and/or Apo-latanoprost-timolol sold (to any jurisdiction) after the expiration of the 132 Patent are attributable to the alleged infringement and/or to the alleged use of the purported invention of the 132 Patent.

19D. In the event that there is a finding of infringement in respect of Apo-latanoprost and/or Apo-latanoprost-timolol sold (to any jurisdiction) *after* the expiration of the 132 Patent, which is expressly denied, and in the event that Pfizer is entitled to elect an accounting of Apotex's profits, which is also expressly denied, then Pfizer is only entitled to the difference, if any, between (a) the profits that Apotex earned on the actual allegedly infringing Apo-latanoprost and/or Apo-latanoprost-timolol sold (to any jurisdiction) *after* the expiration of the 132 Patent; and (b) the hypothetical profits that Apotex could have and would have earned on

non-infringing Apo-latanoprost and/or Apo-latanoprost-timolol sold (to any jurisdiction) after the expiration of the 132 Patent.

19E. It has always been and continues to be Pfizer's burden to prove that, in the absence of the alleged infringement, Apotex could not have and would not have sold any non-infringing Apo-latanoprost and/or Apo-latanoprost-timolol after the expiration of the 132 Patent.

IV. The 132 Patent

20. The 132 Patent, entitled *Prostaglandin* Derivatives *for the Treatment of Glaucoma or Ocular Hypertension*, was filed, without priority, on September 12, 1989.

21. The patentee also filed a supplementary disclosure on January 11, 1991 adding specific additional information to the disclosure and claim set of the '132 Patent which would have the corresponding filing date of January 11, 1991 and not September 12, 1989.

22. Further the patentee filed for correction of an alleged clerical error in claim 1 on June 14, 2002 to add to claim 1 the phrase "a derivative of "just before prostaglandin.

23. The 132 Patent is entitled "Prostaglandin Derivatives for the Treatment of Glaucoma or Ocular Hypertension" and relates to ophthalmological compositions of certain prostaglandin derivatives for use in the topical treatment of glaucoma or ocular hypertension without causing substantial ocular irritation (including feelings of grittiness in the eye and

increased tearing), an irritant effect on the sensory nerves of the cornea and conjunctival hyperemia.

24. The 132 Patent further references a class of compounds, smaller classes of compounds, and specific compounds including latanoprost.

25. The 132 Patent further relates to ophthalmic compositions containing said prostaglandin derivatives (both classes and compounds) and their manufacture and use.

26. The 132 Patent acknowledges the prior disclosure of prostaglandins as treatments for ocular hypertension and glaucoma, but asserts that the usefulness of "some" of those old compounds ~~are~~ is limited by their tendency to cause irritation (including feelings of grittiness in the eye and increased tearing), an irritant effect on the sensory nerves of the cornea, and conjunctival hyperemia. ~~The 132 Patent promises that its compounds, including latanoprost, avoid these problems.~~ Indeed, the 132 Patent concedes that prostaglandins that cause superficial irritation and vasodilation in the conjunctiva lack any "practical usefulness" as they are unsuitable drugs for treating glaucoma or ocular hypertension (132 Patent, p. 3). The purported invention of the 132 Patent is the identification of a subset of previously disclosed prostaglandins, including latanoprost, which are able to treat glaucoma and ocular hypertension because they are physiologically acceptable on account of the fact that they do not cause substantial side effects when administered on a chronic basis.

26A. The 132 Patent in fact disavows and carves out from its purported invention any prostaglandins that are not therapeutically effective (for the treatment of glaucoma or ocular

hypertension) and physiologically acceptable on account of irritation and adverse effects on the eye (132 Patent, p. 7, 19 and 22) on the basis that such compounds lack any "practical usefulness" but nevertheless proceeds to claim prostaglandins, including latanoprost, for which there was no demonstration or sound prediction of therapeutic efficacy and/or physiological acceptability by the filing date and which in fact lack therapeutic efficacy and/or physiological acceptability, contrary to the 132 Patent's clear and unequivocal assertions.

26B. The 132 Patent thus improperly:

(a) claims that the named inventors invented more than they in fact did;

(b) contains a disclosure that is not correct and full;

(c) states unsubstantiated uses or operations of the invention, contrary to subsection 27(3) of the *Patent Act* (and/or section 36 of the *Patent Act* as it existed before 1989); and

(d) claims overly broadly.

26C. The 132 Patent thus suffers from the mischief of "overpromising".

27. The 132 Patent purports to describe studies the inventors performed to demonstrate the properties of the compounds of the 132 Patent, including latanoprost. The patent gives certain results for single dose tests for ocular discomfort in cats, for single dose tests for conjunctival hyperemia in rabbits, and for single dose tests for IOP reduction in monkeys and healthy human volunteers. The 132 Patent contains no test results in any animal or human

subject involving the chronic administration of a test compound, and no test results on animals or humans having ocular hypertension or suffering from glaucoma.

28. The 132 Patent did not pioneer the use of prostaglandins, or even latanoprost, as treatments for glaucoma and ocular hypertension. In the 1970s, Drs. Laszlo Bito and Carl Camras reported that prostaglandins of the $PGF_{2\alpha}$ subtype had an ocular hypotensive effect when applied topically to the eye. By September 1989, numerous prostaglandin derivatives had been synthesized and tested for use as general and ocular hypotensives in the treatment of glaucoma among other pharmacological and therapeutic uses. Commercial chemical companies were formed which synthesized and sold synthetic prostaglandins derivatives for research and therapeutic purposes. By 1986, Canadian Letters Patent No. 1,208,560 (the "560 Patent") had disclosed and claimed a group of prostaglandins, including latanoprost, as treatments for IOP and glaucoma.

28A. Given that the 560 Patent discloses and claims a group of prostaglandins, including latanoprost, as treatments for IOP and glaucoma, the 132 Patent is, by definition, a selection patent. The asserted invention of the 132 Patent is the selection of particular prostaglandins from the genus of the 560 Patent that "introduce[] completely new, unexpected and advantageous qualities...in that the irritating effect in the conjunctiva and cornea is abolished...[and] in that they cause[] considerably less conjunctival hyperemia" (132 Patent, p. 19-20). Without these asserted advantages, the selected prostaglandins of the 132 Patent, including latanoprost, necessarily lack novelty and inventiveness in view of the 560 Patent. However, Apotex alleges that the selected prostaglandins, including latanoprost:

(a) lack a substantial advantage to be secured or disadvantage to be avoided relative to the unselected members of the genus of the 560 Patent;

(b) do not possess the asserted advantages; and /or

(c) do not possess advantages of a special character peculiar to the selected group;

such that the 132 Patent fails to satisfy the three conditions that must be satisfied for a selection patent to be valid.

29. The 132 Patent contains 38 claims, including compound claims, composition claims and use claims for the treatment of glaucoma and ocular hypertension.

30. Latanoprost is known by the following chemical names:

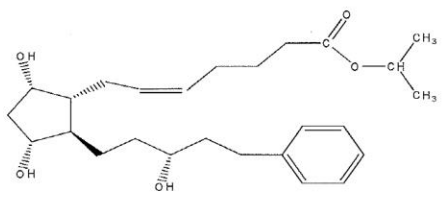
(a) Isopropyl-(Z)-7[(1R,2R,3R,5S)3,5-dihydroxy-2-[(3R)-3-hydroxy-5-phenylpentyl]cyclopentyl]-5-heptenoate

(b) 13,14-dihydro-17-phenyl-18,19,20-trinor-PGF_2 α-isopropyl ester

(c) [1*R*-[1α(Z),2β(R*),3α,5α]]-7-[3,5-Dihydroxy-2-(3-hydroxy-5-phenyl- pentyl) cyclopentyl]-5-heptenoic acid 1-methylethyl ester

(d) 5-Heptenoic acid,7[3,5-dihydroxy-2-(3-hydroxy-5-phenyl- pentyl)cyclopentyl]-1-methylethyl ester, [1R-[1α(Z),2β(R*),3α ,5α]]-

31. Latanoprost has the following structural formula:



32. Apotex states that latanoprost is included within claims 1 - 9, claims 11 and 12 when dependent on claims 1 - 4, 7 and 9, and, claims 18-28, 30-31 and 36-38 of the 132 Patent.

32A. The subject matter of the Asserted Claims of the 132 Patent is as follows:

(a) Claim 12 claims a therapeutic ophthalmological composition containing latanoprost for treatment of glaucoma or ocular hypertension in an amount sufficient to reduce intraocular pressure without causing substantial ocular irritation;

(b) Claim 19 claims latanoprost; and

(c) Claims 31 and 38 claim the use of latanoprost in the treatment of glaucoma or ocular hypertension.

32B. As described above, the problem in the prior art identified by the 132 Patent is that previously disclosed prostaglandins were not useful as treatments for ocular hypertension and glaucoma because of their tendency to cause substantial side effects, including irritation (including feelings of grittiness in the eye and increased tearing), an irritant effect on the sensory nerves of the cornea, and conjunctival hyperemia.

32C. The purported solution provided by the 132 Patent to this problem in the prior art is the identification of prostaglandins (including latanoprost) wherein the omega chain is modified to include a ring structure such that the lowering of IOP is maintained without causing substantial side effects so as to permit the treatment of glaucoma and ocular hypertension on a chronic basis.

32D. Hence, as described above, the subject matter of the invention of the 132 Patent, as claimed, is a subset of previously disclosed prostaglandins, including latanoprost, which are able to treat glaucoma and ocular hypertension because they are physiologically acceptable on account of the fact that they do not cause substantial side effects when administered on a chronic basis (the "invention of the 132 Patent").

V. No Infringement of the 132 Patent

33. For the reasons set out below, Apotex denies that the making, using and selling in Canada of its Apo-Latanoprost solution infringes the 132 Patent, and particularly the Asserted Claims, and puts Pfizer Canada and Pharmacia to the strict proof thereof.

34. Apotex states that its Apo-Latanoprost solution and its use in treating patients for the reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension are in accordance with the teachings of the prior art and/or uninventive (obvious) variations thereof.

35. The 560 Patent taught the skilled addressee to use isopropyl esters of $PGF_{2\alpha}$ to treat glaucoma and ocular hypertension.

36. Latanoprost is a derivative of a lower alkyl ester of $PGF_{2\alpha}$ as taught and claimed in the '560 Patent.

37. By the filing date of the 132 Patent, the preparation and esterification of $PGF_{2\alpha}$ compounds was taught in the art and was regarded as part of the common knowledge of the

person skilled in the art. Esterification was regarded as the most appropriate method for delivery.

38. With the consent, authority and agreement of, *inter alia*, Pharmacia, Pfizer Canada listed the 560 Patent on the Patent Register on June 17, 2003 in respect of XALATAN®. Clearly, in listing the 560 Patent on the Patent List (Document #80) in respect of latanoprost, Pfizer Canada and Pharmacia must have concluded that the subject matter of the claims would be understood by the person skilled in the art in view of his/her common knowledge, to include $PGF_{2\alpha}$ and their derivatives, including latanoprost and compositions containing latanoprost for use to treat glaucoma and hypertension.

39. Apotex asserts that the claims of the 560 Patent, as would be understood by persons skilled in the art, include not only derivatives of $PGF_{2\alpha}$ but also 13,14-dihydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-isopropylester and thus the patentee of the 132 Patent has clearly admitted that latanoprost is within the teachings and claims of the 560 Patent as a suitable $PGF_{2\alpha}$ derivative.

40. Apo-Latanoprost and its use for treatment of glaucoma and ocular hypertension are all in accordance with the teachings of the prior art and uninventive (obvious) variants (non-patentable variations) thereof, having regard to the common knowledge of the person skilled in the art.

41. A valid patent cannot be infringed by a person who practises the prior art in a manner consistent with how a skilled addressee would have done so based on the prior art. Thus,

Apotex cannot infringe the 132 Patent in accordance with the principles enunciated in *Gillette Safety Razor Company v. Anglo Trading Company Ltd.* (1913), 30 R.P.C. 465 (H.L.) known as the "Gillette Defence". This *Gillette* defence ensures that any member of the public can use processes in the public domain without fear of trespassing on the patent rights of another.

42. Otherwise, each of the Asserted Claims of the 132 Patent as well as each of the remaining claims, including claims 1-9, claims 11-12 (dependent on claims 1-4, 7 and 9), claims 18-28, 30-31 and 36-38 of the 132 Patent, is invalid as being anticipated and obvious, as discussed below.

43. Apotex will not directly or indirectly infringe any of the remaining claims for the same reasons.

44. Further Apotex will not infringe any of the remaining claims, claims 10, 13, 14, 15, 29, and 32 to 35 since, when properly construed each of these claims does not include latanoprost, namely each does not include 13,14-dihydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$ - isopropylester, within the scope thereof.

45. To the extent that any of the claims of the 132 Patent are valid, which is not admitted but expressly denied, and they are found to include within their scope any bulk chemical compound or formulation used by Apotex, and Pharmacia and/or Pfizer Canada are not disentitled from seeking any relief under the 132 Patent, Apotex pleads and relies upon the common law "experimental use" exception to infringement. Apotex also pleads and relies upon subsections 55.2(1) and (6) of the *Patent Act*, as they read at all material times, dealing

with the manufacture, construction, use or sale (collectively, for the purposes of paragraph 38 "use") of a patented invention relating to the development of regulatory submissions, private use and experimental use.

46. In this respect, Apotex states that one or more of the foregoing exceptions would exempt from infringement the following uses of latanoprost solution:

(a) use of latanoprost solution for research and development purposes including:

(i) determining the suitability of latanoprost solution;

(ii) the development of formulations containing latanoprost solution;

(iii) the preparation and carrying out of pre-clinical and clinical studies; and

(iv) the preparation and carrying out of bioequivalence testing;

(b) use of latanoprost solution for internal and external quality control purposes; and

(c) use of latanoprost solution in compliance with regulatory requirements specified in the *Food and Drug Regulations* (Canada) (as listed below), as well as the provincial regulatory requirements (section 6 of Regulation 935, *Drug Interchangeability and Dispensing Fee Act* (Ontario)), which requirements relate to:

(v) materials used to generate bioequivalence and safety data for submission (subsection C.08.002.1(2));

(vi) materials used to generate supplemental ANDS data (subsection C.08.004(2));

(vii) retained samples for ANDS (subsection C.08.002.1(3));

(viii) information which may be required by the Director of Health Canada (subsections C.08.002.1 (2)-(3) and section C.08.008);

(ix) materials consumed in raw material testing (section C.02.009);

(x) initial testing (subsection C.02.009 (1) and (2));

(xi) updated testing (C.02.009 (4));

(xii) retained samples (subsection C.02.025 (2));

(xiii) materials consumed in specification development (subsection C.02.011 (1));

(xiv) materials retained for or used in testing specification compliance (subsection C.02.011 (2)) and section C.02.020);

(xv) materials retained for ongoing information control (sections C.02.012 and C.02.020);

(xvi) materials consumed in quality control process development (section C.02.015 (1));

(xvii) materials retained for ongoing quality control (section C.02.014 and subsection C.02.015 (3));

(xviii) materials rejected by quality control (section C.02.014);

(xix) materials consumed in specification development (section C.02.018);

(xx) materials retained for or used in testing specification compliance (section C.02.019);

(xxi) materials rejected for non-compliance with specification (subsection C.02.018 (2); and

(xxii) retained samples for stability testing (section C.02.028)

VI. The 132 Patent and Its Claims are Invalid, Void and of No Force or Effect

47. In the alternative, if the argument that Apo-Latanoprost solution infringes one or more of the Claims in Issue is pertinent, and if Apotex's Apo-Latanoprost solution is found to be within the scope of any one of the claims of the 132 Patent, including specifically the Asserted Claims, all of which is specifically denied, Apotex's Apo-Latanoprost solution could not infringe any of these claims because the 132 Patent, and all of its claims, is invalid, void and of no force

or effect. Documents relevant to Apotex's invalidity pleading are listed in Schedule "A" attached hereto.

48. In particular, each of the claims of the 132 Patent is invalid for the reasons that follow (in addition to what was asserted above).

a. Failure to Pay the Prescribed Final Fee

49. The 132 Patent issued on July 29, 1997 from an application that was filed in the Canadian Patent Office ("CPO") on September 12, 1989 and was assigned serial number 611,003 ("003 Application").

50. Apotex states that the 132 Patent is, and has always been, invalid, void and of no force or effect because the 003 Application from which the 132 Patent issued was forfeited by the applicant and was deemed abandoned for failure to pay the prescribed final fee, and the forfeited and abandoned application were not at any material time restored or reinstated by the applicant or made the subject of any rectifying payment pursuant to section 78.6 of the *Patent Act*.

51. At the time of filing of the 003 Application on September 12, 1989, the applicant submitted the following documents to CPO:

(a) a cover letter dated September 12, 1989 from the agents appointed by the applicant;

(b) a Petition dated September 7, 1989 that named Johan W. Stjernschantz and Bahram Resul as inventors, and Pharmacia AB as applicant. The Petition was signed by the applicant;

(c) a specification, including claims (together with a second copy of the claims);

(d) two copies of an Abstract;

(e) an Assignment dated September 11, 1989 from the inventors to the applicant; and

(f) a cheque in the amount of $400.00.

52. The cover letter indicated that a "Petition Supplementary Sheet claiming small entity status" was not included in the application, and the Petition did not include an indication that the applicant claimed small entity status. The cheque for $400.00 covered the payment of the assignment recordal fee of $100.00 and the filing fee for a large entity of $300.00. At the time of filing the 003 Application, the applicant did not claim to be, nor was it in fact, a small entity within the meaning of the *Patent Act* and *Patent Rules* then in force.

53. Between September 12, 1989 and November 19, 1996, the 003 Application was subject to examination by CPO, and was in fact examined. The applicant, on various occasions during this period, amended the specification and/or claims of the 003 Application, either voluntarily or in response to a requisition by the examiner. The 003 Application was eventually allowed and a Notice of Allowance dated November 19, 1996 was sent to the applicant.

54. During the period between September 12, 1989 and November 19, 1996, the applicant Pharmacia AB underwent several corporate reorganizations, including mergers with other entities. As a result, the applicant of the 003 Application filed with CPO certain merger documents and assignments. At all material times, the applicant was not in fact, nor did the applicant claim to be, a small entity or a small business concern within the meaning of the *Patent Act* and *Patent Rules* then in force.

55. The Notice of Allowance dated November 19, 1996 advised the applicant of the following:

(a) "The above application for patent has been found allowable."

(b) "The final fee of THREE HUNDRED AND FIFTY DOLLARS ($350.00) or SEVEN HUNDRED DOLLARS ($700.00) depending upon small entity status, must be paid no later than SIX MONTHS of the data of this notice."

56. As a result of the issuance of the Notice of Allowance dated November 19, 1996 and of the provisions of section 73 of the *Patent Act*, the applicant had 6 months (until May 19, 1997) within which to pay the prescribed final fee of $350.00 or $700.00 depending on whether the applicant qualified as a small entity.

57. In response to the Notice of Allowance and prior to the deadline of May 19, 1997, the applicant filed two letters with CPO, as follows:

(a) a letter dated March 17, 1997 in which the applicant purported to pay the final fee, and stated:

"The sum of $300.00 is included in our cheque No. 12650 of today's date in payment of the final fee for the above application."

(b) a letter dated April 18, 1997 in which the applicant purported to pay an additional amount in respect of the final fee, and stated:

"Further to our letter of March 17, 1997 responding to the Notice of Allowance, we advise that our Cheque No. 12708 of today's date includes the sum of $50.00 in payment of the balance owing on the final fee for the above application.

Due to a purely clerical oversight, payment of only $300.00 was made on March 17 (our Cheque No. 12650 of that date). We apologize for the inconvenience and look forward to the issuance of the patent in due course."

58. No further payments in response to the Notice of Allowance were made by the applicant prior to May 19, 1997, so that the applicant paid the total amount of $350.00 as the final fee. CPO accepted the applicant's payment of $350.00 as the final fee and the 132 Patent issued on July 29, 1997.

59. At all material times from September 12, 1989 (when the 003 Application was filed) through to February 1, 2007 (when rectifying payments pursuant to section 78.6 of the *Patent Act* could be made), the applicant of the 003 Application and the patentee of the 132 Patent did not claim to be, nor did they qualify as small business concerns or small entities within the meaning of the *Patent Act* and *Patent Rules* then in force.

60. Accordingly, in response to the Notice of Allowance, the applicant was required to pay the prescribed final fee as a large entity. Subsections 30(1) and 30(5) and Schedule II of the *Patent Rules*, SOR/96-423 required the applicant, as a large entity, to pay the prescribed

final fee of $700.00. The applicant, however, only paid $350.00 as the final fee prior to the deadline of May 19, 1997. The applicant and patentee did not make any further payments of any kind in respect of the Notice of Allowance and the prescribed final fee at any time thereafter, up to and including February 1, 2007.

61. By reason of the foregoing, Apotex alleges that the applicant of the 003 Application failed to pay the prescribed final fee of $700.00, as required of a large entity, contrary to section 73 of the *Patent Act*, as amended, and sections 3 and 30 of the *Patent Rules*, SOR/96-423. Pursuant to subsection 73(1) of the *Patent Act*, as amended, and subsection 78.2(2) of the *Patent Act*, the failure of the applicant to pay the prescribed fee within six months of the date of the Notice of Allowance resulted in the 003 Application becoming forfeited as of May 20, 1997.

62. An application that is forfeited in accordance with subsection 73(1) of the *Patent Act* can only be restored if the applicant complies with the requirements of subsection 73(2) of the *Patent Act*. At no time has the applicant for the 003 Application filed an application to restore the forfeited 003 Application and paid the prescribed further fee as required by subsection 73(2) of the *Patent Act*.

63. In addition, Apotex alleges that the failure of the applicant to pay the prescribed final fee of $700.00, as required of a large entity, contrary to section 73 of the *Patent Act*, resulted in the 003 Application being deemed abandoned as of May 20, 1997 pursuant to subsection 30(1) of the *Patent Act* and subsection 78.2(2) of the *Patent Act*.

64. An application that is deemed abandoned in accordance with subsection 30(1) of the *Patent Act* can only be reinstated if the applicant complies with the requirements of subsection 30(2) of the *Patent Act*. At no time has the applicant for the 003 Application petitioned CPO to reinstate the abandoned 003 Application and paid the prescribed further fee as required by subsection 30(2) of the *Patent Act*.

65. Moreover, at no time prior to or on February 1, 2007 has the applicant for the 003 Application or the patentee of the 132 Patent submitted to CPO any further payments, including a further payment of $350.00, pursuant to section 78.6 of the *Patent Act*. Instead, the patentee, by letter dated October 23, 2006, advised CPO that:

> "Pursuant to Section 78.6 of the *Patent Act*, we advise that the entity status of this patent is large."

66. Although the patentee referred to section 78.6 of the *Patent Act*, the patentee did not avail itself of the right pursuant to section 78.6 to make a further payment of $350.00. As a result, the amount paid by the applicant as the final fee was only $350.00 instead of the prescribed amount of $700.00.

67. At all material times, the Commissioner of Patents and CPO had no authority under the *Patent Act* or *Patent Rules* in force to waive or reduce the prescribed final fee, nor did the Commissioner of Patents or CPO have any authority to extend the deadline for paying the prescribed final fee in the required amount or to accept any further payment, or for seeking

restoration or reinstatement, none of which was requested or done by the applicant or patentee in any event.

68. As a result of the foregoing, the 003 Application was forfeited and was deemed to be abandoned as of May 19, 1997 on the basis that the applicant failed to pay the prescribed final fee of $700.00 as a large entity. The forfeited and abandoned application was never restored or reinstated as required by the *Patent Act*, and applicant for the 003 Application or the patentee of the 132 Patent never made any further payments pursuant to section 78.6 of the *Patent Act*. Because the 003 Application was, by operation of the *Patent Act*, forfeited and abandoned, the 132 Patent could not have validly been issued and granted. Consequently, the 132 Patent is and has always been invalid, void and of no force or effect.

b. Double Patenting

69. Apotex states that the claims of the 132 Patent, including specifically the Asserted Claims, is invalid, void and of no effect for claiming the same invention as previously claimed in the 560 Patent or a non-inventive variant thereof.

70. The claims of the 560 patent cover, among other things, a "composition for the topical treatment of glaucoma in the eye of a primate subject comprising an effective amount of a lower alkyl ester of $PGF_{2\alpha}$ or derivative thereof and an ophthalmically compatible carrier" (claim 1); wherein the $PGF_{2\alpha}$ derivative is a C1 to C5 alkyl ester of $PGF_{2\alpha}$ (claim 2); wherein the $PGF_{2\alpha}$ derivative is, among other things, a $PGF_{2\alpha}$ isopropyl ester (claim 3); and wherein the composition contains about 0.01% to about 2.0% of a C1 to C5 alkyl ester of $PGF_{2\alpha}$ derivative

(claim 4). A skilled addressee would recognize that latanoprost is among the compounds claimed for inclusion in a topical composition for treatment of glaucoma in primates (i.e. including humans).

71. As noted, the Asserted Claims of the 132 Patent cover this same subject matter. While claim 12 specifies that its composition function "without causing ocular irritation," this is a property inherent in the composition that would be immediately apparent upon its use. Further, and as noted above, the 560 patent taught that its compositions would be without significant side effects and also taught that the lid-closure response of $PGF_{2\alpha}$ esters was not noticeable in monkeys. A skilled addressee looking at the claims of the 560 Patent would have arrived at the subject matter of the claims of the 132 Patent without invention. There is thus no patentable distinction between the claims of the 560 Patent and the impugned claims of the 132 Patent.

72. To Apotex's present knowledge, one or more of Pharmacia or Pfizer Canada, their related companies or their predecessors in title had the following interactions with the Minister in relation to XALATAN:

(a) On a date unknown to Apotex but known to the Defendants, Pharmacia & Upjohn Inc. filed a new drug submission ("NDS") under the FDA Regulations ("NDS #1") with respect to XALATAN;

(claim 4). A skilled addressee would recognize that latanoprost is among the compounds claimed for inclusion in a topical composition for treatment of glaucoma in primates (i.e. including humans).

71. As noted, the Asserted Claims of the 132 Patent cover this same subject matter. While claim 12 specifies that its composition function "without causing ocular irritation," this is a property inherent in the composition that would be immediately apparent upon its use. Further, and as noted above, the 560 patent taught that its compositions would be without significant side effects and also taught that the lid-closure response of $PGF_{2\alpha}$ esters was not noticeable in monkeys. A skilled addressee looking at the claims of the 560 Patent would have arrived at the subject matter of the claims of the 132 Patent without invention. There is thus no patentable distinction between the claims of the 560 Patent and the impugned claims of the 132 Patent.

72. To Apotex's present knowledge, one or more of Pharmacia or Pfizer Canada, their related companies or their predecessors in title had the following interactions with the Minister in relation to XALATAN:

(a) On a date unknown to Apotex but known to the Defendants, Pharmacia & Upjohn Inc. filed a new drug submission ("NDS") under the FDA Regulations ("NDS #1") with respect to XALATAN;

(b) On or about July 26, 1995, Robert J. Little, on behalf of Pharmacia Inc., filed a Form IV patent list under the *PMNOC Regulations* ("Form IV #1") in respect of NDS #1. In the Form IV #1, Phamacia Inc., among other things:

(i) Indicated "Latanoprost" as the active medicinal ingredient;

(ii) Indicated the '560 Patent as the relevant patent;

(iii) Indicated that it held an exclusive license under the '560 Patent; and

(iv) Certified that the information in the patent list was accurate.

(c) On or about June 16, 1997, the Minister issued an NOC to Pharmacia & Upjohn Inc. in respect of NDS #1 ("NOC #1");

(d) On a date unknown to Apotex but known to the Defendants, Pharmacia Inc. filed an NDS under the *FDA Regulations* ("NDS #2") with respect to XALATAN;

(e) On or about February 13, 2001, the Minister issued an NOC to Pharmacia Inc. in respect of NDS #2 ("NOC #2");

(f) On a date unknown to Apotex but known to the Defendants, Pharmacia Canada Inc. filed a supplement to a new drug submission ("SNDS") under the *FDA Regulations* ("SNDS #1") with respect to XALATAN;

(g) On or about January 28, 2002, Pharmacia Canada Inc. filed a Form IV patent list under the *PMNOC Regulations* ("Form IV #2") in respect of SNDS #1. In the Form IV #2, Pharmacia Canada Inc., among other things:

(i) Indicated "Latanoprost" as the active medicinal ingredient;

(ii) Indicated "XALATAN" as the brand name;

(iii) Indicated the '560 Patent as the relevant patent;

(iv) Indicated that it held an exclusive licence under the '560 Patent; and

(v) Certified that the information in the patent list was accurate;

(h) On or about April 25, 2003, the Minister issued an NOC to Pharmacia Canada Inc. in respect of SNDS #1 ("NOC #2").

73. Apotex states that all of the foregoing interactions with the Minister were taken with the consent, authority and agreement of the Defendants herein and/or their predecessors in title.

74. Apotex further states that, in filing and/or in consenting, authorizing and agreeing to file Form IV #1 and Form IV #2, Pfizer Canada and Pharmacia publicly certified that the information therein was accurate and that the 560 Patent met the eligibility requirements under subsections 4(2) and 4(3) of the *Patent Regulations*, all of which require, among other

things, that the patent contain, in some respect, a claim to the medicinal ingredient indicated in the Form IV patent list in question.

75. In this instance, by filing Form IV #1 and Form IV #2, Pfizer Canada and Pharmacia publicly certified, among other things, that the 560 Patent claims (and, therefore, encompasses) latanoprost.

76. Apotex states that, in making these certifications and filing Form IV #1 and Form IV #2, Pfizer Canada and Pharmacia elected to take advantage of the machinery of the *Patent Regulations* and benefited thereby.

77. Having publicly certified that the 560 Patent claims latanoprost and having enjoyed the benefits of the *Patent Regulations* in relation thereto, it would be inequitable for Pfizer Canada and Pharmacia to be able to take the position in this case that the 560 Patent does not disclose and claim latanoprost.

78. Stated alternatively, Apotex states that Pfizer Canada and Pharmacia are estopped from denying that the 560 Patent does cover and claim latanoprost.

79. Apotex also states that Pfizer Canada's and Pharmacia's inclusion of the 560 Patent on its Patent List for latanoprost is an admission upon which the public and Apotex are able to rely and thus that the 560 Patent contains a claim for latanoprost as being a derivative of a $PGF_{2\alpha}$.

80. The purportedly novel compounds claimed in the 132 Patent are for the same invention and use as was previously known and would be previously known by the person skilled in the art, *i.e.*, the treatment of glaucoma and ocular hypertension and thus constitute same invention double patenting or obvious-type double patenting, constituting an obvious variant of the subject matter of the claims of the 560 Patent.

c. Lack of Novelty/Anticipation

81. Apotex asserts that each of the claims of the 132 Patent, including specifically the Asserted Claims, is anticipated and thus invalid, void and of no effect in view of the teachings of each of the following:

(a) E. Granstörm, Vol. 9, No. 1, "Metabolism of 17-Phenyl-18,19,20-Trinor Prostaglandin F2α In The Cynomolgus Monkey And The Human Female", Prostaglandins, teaches the preparation of prostaglandin derivatives. Especially it teaches the preparation of 13,14 Dihydro -17- phenyl-18,19,20- trinor- $PGF_{2\alpha}$;

(b) E. Granstörm, Vol. 1, "Effect of Chemical Modifications On The Metabolic Transformation of Prostaglandins", Advances in Prostaglandin and Thromboxane Research teaches the preparation of prostaglandin derivatives. Specifically it teaches the preparation of 13,14 Dihydro -17- phenyl-18,19,20- trinor- $PGF_{2\alpha}$;

(c) M. Ross Johnson, Thomas K. Schaaf, Jay W. Constantine and Hans-Jurgen Hess, Vol. 20, No. 3, "Structure Activity Studies Leading To A Tissue-Selective

Hypotensive Prostaglandin Analog, 13,14-Dihydro-16-Phenyl-ω-Tetranor PGE2", Prostaglandin, teaches the preparation of prostaglandin derivatives substituted with phenyl ring on the ω-chain. It also teaches the relation between the position of the phenyl ring and the hypotensive activity of the prostaglandins;

(d) The 560 Patent teaches a composition for the topical treatment of glaucoma by administration of isopropyl ester of the $PGF_{2\alpha}$ derivatives including latanoprost by Pfizer's own admission; and

(e) US patent 4,131,738 "6-Hydroxy-PGE1 Compounds" published on December 26, 1978, teaches prostaglandins substituted with a phenyl ring on the ω-chain. It also teaches use of those compounds for reduction of intraocular pressure without localized side effects such as irritation.

82. All the information needed by one skilled in the art to produce the alleged claimed invention of the 132 Patent is available to one skilled in the art in the teachings of each of these documents without the exercise of any inventive skill.

82A. Should Pfizer assert that the 132 Patent is not a selection patent (from the genus of the 560 Patent), then Pfizer is precluded from relying on any of the asserted "new, unexpected and advantageous qualities" (132 Patent, p. 19) of the compounds described and claimed in the 132 Patent such that the 132 Patent and all of the Asserted Claims are necessarily anticipated by the 560 Patent.

d. Obviousness

~~83. Apotex further asserts that the subject matter, invention and/or inventive concept of the 132 Patent, including specifically the Asserted Claims, is obvious and thus invalid, void and of no effect.~~

82B. Apotex further asserts that the invention of the 132 Patent, as defined above, was obvious.

82C. Should Pfizer take the position that the invention is something other than the invention of the 132 Patent, as defined above, including, but not limited to (i) the identification of prostaglandins that lower IOP; and/or (ii) the identification of prostaglandins that treat glaucoma and ocular hypertension without eliminating the substantial side effects caused by previously disclosed prostaglandins, then Apotex alleges that Pfizer's purported invention was also necessarily obvious at all material times.

~~120.~~ 82D. Apotex relies on the state of the art and common knowledge of a person skilled in the art set out herein including the teachings of those documents which were previously referenced above and the teachings of all of the prior art documents listed in Schedule "A", all of which teachings comprise part of the common knowledge of the person skilled in the art.

~~121.~~ 82E. The teachings of the documents referred to in Schedule "A" form part of the common knowledge of the person skilled in the art and set out the common knowledge of

persons skilled in the art prior to September 12, 1989, the Canadian filing date of the 132 Patent.

~~122.~~ 82F. Persons skilled in the art would therefore be led directly and without difficulty to the subject matter of the 132 Patent, including specifically the Asserted Claims, without the exercise of any inventive ingenuity whatsoever based on the common knowledge of the person skilled in the art as exemplified by the teachings of the documents of Schedule "A".

~~123.~~ 82G. The common knowledge in the art with respect to the use of prostaglandins and derivatives for ophthalmic uses including glaucoma treatment and ocular hypertension included, but were not limited:

(a) PGA, PGB, PGD, PGE and $PGF_{2\alpha}$. were known;

(b) Derivatives thereof having the alpha chain including alkyl esters including isopropyl esters for use to treat glaucoma and ocular hypertension were known;

(c) $PGF_{2\alpha}$ methyl esters when administered to the eye resulted in hydrolysis thereof producing small amounts of undesired methanol thus requiring the skilled person to use, as part of the common knowledge. Thus $PGF_{2\alpha}$ and derivatives thereof with an ethyl or isopropyl ester with the isopropyl ester were preferred;

(d) All known PGA, PGB, PGD, PGE and $PGF_{2\alpha}$ and derivatives known prior to the issue of the 560 Patent would be known by the person skilled in the art to be

useful for the treatment of glaucoma and ocular hypertension given the teachings of the 560 Patent whose teachings formed part of the common knowledge of the person skilled in the art;

(e) All known PGA, PGB, PGD, PGE and $PGF_{2\alpha}$ and derivatives known subsequent to the issue of the 560 Patent but prior to the filing of the 132 Patent in Canada, would be known by the person skilled in the art to be useful for the treatment of glaucoma and ocular hypertension given the teachings of the 560 Patent whose teachings formed part of the common knowledge of the person skilled in the art;

(f) $PGF_{2\alpha}$ esters and derivatives of $PGF_{2\alpha}$ as esters including the isopropyl ester comprised the most suitable agents for the topical treatment of glaucoma. Latanoprost was known;

(g) $PGF_{2\alpha}$ and isopropyl esters of $PGF_{2\alpha}$ were preferred to lower IOP and treat glaucoma;

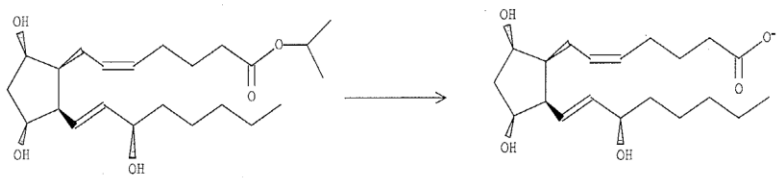
(h) Esterification of the carboxyl group of $PGF_{2\alpha}$ enhanced ocular hypotensive potency;

(i) Reduction of the double bond to single bond at Carbons 13 and 14 was known;

(j) 17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$ and 13,14-dihydro-17-phenyl-18,19,20-trinor-PGF analogues were known;

(k) The ocular irritation test, lid-closure response in respect of ocular discomfort, was known;

(l) It was known that prostaglandin esters would hydrolyze *in vivo* to release the free acid form as illustrated below:



(m) Prostaglandins and specifically $PGF_{2\alpha}$ and derivatives were taught and known to reduce intraocular pressure and to be used for treatment of glaucoma;

(n) Irritation to the eye as a result of administration of prostaglandins and its derivatives was known;

(o) Substitutions of a phenyl ring at the 16 and 17 position of the ω-chain were known for prostaglandin derivatives;

(p) Prostaglandin compounds with the omega chain containing "13-14-dihydro-17 phenyl -18, 19-20 trinor" and specifically $PGF_{2\alpha}$ were known;

(q) $PGF_{2\alpha}$ and its derivatives were the preferable agents for reduction of intraocular pressure, in relation to other PGs, for example as taught in the 560 Patent;

(r) The esters of prostaglandin resulted in PG analogs more soluble in lipids and thus these analogs had better solubility in ophthalmic vehicles and better penetration into the eye, improving the potency for intraocular pressure reduction;

(s) Isopropyl esters were the most preferred derivatives of the prostaglandins for long term ocular use;

(t) Prostaglandins and their derivatives especially $PGF_{2\alpha}$ derivatives were successfully tested for the reduction of intraocular pressure in cats, monkeys, and humans;

(u) Prostaglandin esters are more readily absorbed into the eye due to higher lipophilicity;

(v) The isopropyl ester was found to be the preferred prostaglandin derivative and particularly $PGF_{2\alpha}$ isopropyl esters and derivatives of $PGF_{2\alpha}$ isopropyl esters;

(w) Prostaglandins substituted with a phenyl ring are more potent than natural prostaglandins especially substitution of the phenyl ring at the 17 position for the treatment of glaucoma and ocular hypertension;

(x) It was known to administer PGF_2 isopropyl esters and derivatives (including known derivatives in the art including a phenyl ring in the 16 and 17 positions) to the eyes of those suffering from glaucoma caused by high intraocular pressure;

(y) It was known that some prostaglandins have more severe side effects than others, while other prostaglandin derivatives did not have significant side effects at all;

(z) Prostaglandin derivatives with 13-14-dihydro-17 phenyl -18,19-20 trinor substitution on the omega chain and particularly $PGF_{2\alpha}$ with those substitutions were known;

(aa) The saturation of the double bond at the 13-14 position of a prostaglandin was a well known procedure as well as a naturally occurring procedure; and

(bb) Techniques for production of prostaglandin derivatives with or without double bonds at the 13-14 position were known.

~~124.~~ 82H. The compounds referenced above included the omega chain of these prostaglandins and their derivatives, with a phenyl ring at the 17-position prior to September 12, 1989, namely the filing date. These compounds were known to have reduced side effects when compared to those prostaglandins lacking the phenyl ring.

~~125.~~ 82I. As demonstrated by the above teachings, persons skilled in the art would be aware (a) that prostaglandins produce side effects in the eye; (b) that isopropyl ester derivatives of prostaglandins produced less side effects than natural prostaglandins; (c) prostaglandins substituted with a phenyl ring did not produce side effects; and (d) prostacyclins substituted with a phenyl ring did not produce side effects. Persons skilled in the art would

select a prostaglandin derivative substituted on the omega chain with a phenyl ring and on the alpha chain with an isopropyl ester such as those known in the art and were part of the common knowledge of the person skilled in the art or obvious variants thereof.

~~126.~~ 82J. The person skilled in the art as part of his/her common knowledge in the art would know that, in order to treat glaucoma and minimize side effects, ~~knew~~ to choose to administer derivatives of $PGF_{2\alpha}$ isopropyl esters including the isopropyl ester (and including a phenyl ring in the 16 and 17 position), to the eyes of those suffering from glaucoma caused by high intraocular pressure without the exercise of any inventive ingenuity whatsoever.

~~127.~~ 82K. As a result of the foregoing, Apotex states that the subject matter of the claims of the 132 Patent was obvious to a person skilled in the art contrary to the provisions of sections 2 and 28.3 of the *Patent Act* having regard to the common general knowledge of a person skilled in the art and to the state of the art at the relevant time. Apotex relies on the documents listed in Schedule "A" hereto as evidencing the common general knowledge of a person skilled in the art and the state of the art at the relevant time. Each of the Schedule "A" documents was publicly available as at the relevant time and would have been located by the person skilled in the art performing a diligent search.

e. Inutility

82L. In the alternative to Apotex's allegation that the invention of the 132 Patent, as defined above, was obvious, Apotex asserts that the invention of the 132 Patent was not demonstrated or soundly predicted by the filing date and was also never achieved. Thus, all of

the Asserted Claims of the 132 Patent are invalid for lack of utility at the filing date and lack of utility in fact.

82M. As admitted by the 132 Patent, there can be no practical usefulness for prostaglandins that merely lower intraocular pressure without being capable of treating glaucoma or ocular hypertension without causing substantial side effects.

82N. Thus, the only potential practical purpose and/or potential relevant use is the chronic administration of latanoprost for the treatment of glaucoma and elevated intraocular pressure, without causing substantial side effects.

82O. All of the Asserted Claims are invalid due to (i) the fact that, by the filing date, it had not been demonstrated or soundly predicted that latanoprost could be chronically administered for the treatment of glaucoma and elevated intraocular pressure, without causing substantial side effects; and/or (ii) the fact that latanoprost cannot be chronically administered for the treatment of glaucoma and elevated intraocular pressure, without causing substantial side effects.

82P. While not admitted and expressly denied, at most, the inventors of the 132 Patent achieved a laboratory curiosity whose only possible claim to utility is as a starting material for further research. Should Pfizer assert any use other than chronic administration for the treatment of glaucoma and elevated intraocular pressure, without causing substantial side effects, Apotex alleges that said use asserted by Pfizer:

(a) does not amount to a practical purpose;

(b) is not an actual relevant use (*i.e.*, related to the subject matter of the invention, as claimed);

(c) is no more than as a starting material for further research; and/or

(d) renders the Asserted Claims of the 132 Patent both anticipated and obvious.

Lack of Utility In Fact

83. The claims of the 132 Patent embrace a number of compounds that ~~do not provide the promised and claimed reduction in side effects purported by the 132 Patent~~ cannot, in fact, be chronically administered for the treatment of glaucoma and elevated intraocular pressure, without causing substantial side effects. Apotex alleges that the claims to omega-chain ring-substituted prostaglandin A, B, D, E, or F derivatives having alleged utility in the treatment of glaucoma or ocular hypertension are without merit.

84. Additionally, some of the claimed derivatives in the 132 Patent are inoperative, having no utility, and do not ~~fulfill the promise of~~ provide~~ing~~ a solution to the problem of side effects based on the patentee's own admissions in the 132 Patent and yet the patentee retained these inoperative derivatives in the claims of the 132 Patent, as being appropriate selected members.

85. The 132 Patent admits at page 7, line 8:

> The invention thus relates to the use of certain derivatives of PGA, PGB, PGD, PGE and PGF for the treatment of glaucoma or ocular hypertension. Among these derivatives defined above it has been found that some are irritating or otherwise not optimal, and in certain cases not even useful due to adverse effects and these are excluded in that the group of prostaglandin derivatives defined above is limited to therapeutically effective and physiologically acceptable derivatives. So is for instance (1) 16-phenyl-17,18,19,20-tetranor-PGF2α-isopropyl ester irritating while this can be eliminated by substituting the phenyl ring with a methoxy group giving formula (8) which represent a therapeutically more useful compound.

86. Clearly by the patentee's own admission, not all claimed compounds possess ~~the utility promised by the 132 Patent~~ a practical purpose and/or a relevant use. In fact, as stated above, some were still irritating, for instance 16-phenyl-17,18,19,20-tetranor-PGF2α-isopropyl ester.

87. The 132 Patent within its disclosure admits to claiming compounds which ~~do not fulfill the promise of the patent and thus~~ have no utility in the treatment of glaucoma or ocular hypertension.

88. Further, the Product Monograph for XALATAN® (latanoprost), concedes that XALATAN® still possesses many ~~of the~~ disadvantages and substantial side effects ~~promised to be overcome by the 132 Patent~~, including ocular irritation as follows.

89. Further, in a communication from the Patent Department of Kabi Pharmacia to the European Patent Office, dated November 11, 1992, in regards to corresponding European Patent Application 364,417, the applicants sought to overcome a rejection by the examiner by submissions including experimental data. At page 2 of the submissions, it is stated:

> *The Examining Division has further rejected certain claims for lack of inventive step and further requested comparative tests which should involve a comparison with the closest state of the art, which, according to the position taken regarding document D3 [EP 308135]* **(Document #31)** *which would be a cyclohexyl or cyclopentyl derivative.*

17-cyclohexyl-18,19,20-trinor PGF2α-IE (IE – isopropylester) was therefore tested in comparison with the corresponding 17-phenyl-18,19,20-trinor PGF2α-IE, a derivative according to the present claims. The results are presented in Table 1 where the number of experiments (n) is 5-7 in the various groups. Values for unsubstituted PGF2α-IE, a basic prior art substance, are also given.

The irritative effect was studied in cats using a behavioural model. The intraocular pressure reducing effect was studied in cynomolgus monkeys using pneumatonometry and the conjunctival (surface) hyperemic effect was studied in rabbits eyes. It should be noticed that particularly the monkey model utilized in these tests is very relevant with regard to the selection of drug candidates for human use.

Table 1.

Compound	Dose (µg)	Irritation Score	Reduction in IOP (mm Hg)	Hyperemia Score
17-phenyl PGF2α-IE	0.5			1.8 ± 0.3
	1	0.0 ± 0.0	3.3 ± 0.8*	
	3	0.2 ± 0.2	3.9 ± 0.4*	
	5	0.2 ± 0.2		
17-cyclohexyl PGF2α-IE	0.5			1.4 ± 0.4
	1	0.3 ± 0.1*		
	3	0.8 ± 0.4*	1.0 ± 0.7	
	10	0.7 ± 0.2*	1.5 ± 0.2*	
PGF2α-IE	0.1			2.8 ± 0.2
	1	2.7 ± 0.2*	2.5 ± 0.3*	

* $p<0.05$

It can be concluded that 17-phenyl-18,19,20-trinor PGF2α-IE is unequivocally more potent than 17-cyclohexyl-18,19,20-trinor PGF2α-IE in reducing intraocular pressure in monkeys, and in addition, which is clinically very important: all doses of 17-cyclohexyl-18,19,20-trinor-PGF2α-IE used caused statistically significant ($p<0.05$) ocular irritation, which was not caused by 17-phenyl-18,19,20-trinor-PGF2α-IE.

Both 17-phenyl-18,19,20-trinor PGF2α-IE and 17-cyclohexyl-18,19,20-trinor PGF2α-IE caused slight conjunctival hyperemia as studied in rabbits but this is of minor clinical significance.

> *The overall conclusion is that 17-phenyl-18,19,20-trinor PGF2α-isopropylester, being more potent and causing no ocular irritation, is superior to the corresponding 17-cyclohexyl-18,19,20-trinor PGF2α-isopropylester.* [Emphasis provided with underlining]

90. Thus, even the patentee has admitted the inutility of representative members of the class of omega-chain ring-substituted prostaglandins derivatives ~~(failing to meet the promise of the 132 Patent), a class promised by the 132 Patent to have utility in the treatment of glaucoma or ocular hypertension in the absence/mitigation of side effects~~. Thus, ~~the purportedly new properties promised by the 132 Patent, namely~~ the elimination of side effects with retention of ability to lower IOP~~,~~ is not valid for all omega-chain ring-substituted prostaglandin derivatives.

91. Even the selected 17-phenyl-18,19,20 trinor $PGF_{2\alpha}$ isopropyl ester still had side effects, albeit to a lesser degree or extent~~, contrary to the promise of the patent~~.

92. Furthermore, even in the class of phenyl-substituted prostaglandin derivatives, there are included useless derivatives for the treatment of glaucoma or ocular hypertension.

93. The claims of the 132 Patent are therefore invalid as including variants therein which lack utility and are inoperative ~~and do not yield the promised benefits identified in the disclosure of the 132 Patent~~.

93A. The subject matter of claim 12 (which claims a therapeutic ophthalmological composition containing latanoprost for the treatment of glaucoma or ocular hypertension in an amount sufficient to reduce intraocular pressure without causing substantial ocular irritation) causes substantial ocular irritation and thus cannot be used for the treatment of glaucoma or

ocular hypertension in an amount sufficient to reduce intraocular pressure without causing substantial ocular irritation.

93B. The subject matter of claim 19 (which claims latanoprost) causes substantial ocular irritation and thus cannot be used for the treatment of glaucoma or ocular hypertension in an amount sufficient to reduce intraocular pressure without causing substantial ocular irritation. Should Pfizer assert a use for the subject matter of claim 19 other than chronic administration for the treatment of glaucoma or ocular hypertension in an amount sufficient to reduce intraocular pressure without causing substantial ocular irritation, then the use asserted by Pfizer does not amount to a practical purpose or an actual relevant use such that the subject matter of claim 19 is devoid of utility. As admitted by the 132 Patent, there can be no practical usefulness for prostaglandins that merely lower intraocular pressure without being capable of treating glaucoma or ocular hypertension.

93C. The subject matter of claim 31 (which claims the use of latanoprost in the treatment of glaucoma or ocular hypertension) causes substantial ocular irritation and thus cannot be used for the treatment of glaucoma or ocular hypertension.

93D. The subject matter of claim 38 (which claims the use of latanoprost in the treatment of glaucoma or ocular hypertension) causes substantial ocular irritation and thus cannot be used for the treatment of glaucoma or ocular hypertension.

No Demonstrated Utility / Lack of Sound Prediction

94. In order for there to have been an invention, the purported inventors must have~~,~~ ~~as at the date of invention,~~ demonstrated ~~utility~~ or ~~have~~ soundly predicted ~~the~~ a ~~utility of the subject-matter of the claims~~ practical purpose and/or an actual relevant use for the invention as of the filing date.

95. ~~The utility promised by the 132 Patent is chronic use of the compounds described and claimed therein, including latanoprost, for the treatment of a chronic medical condition. More particularly, the 132 Patent promises that latanoprost, when administered on a chronic basis, reduces intraocular pressure without causing substantial side effects.~~

96. Apotex states that, at the time of filing of the 132 Patent application, the purported inventors thereof had not demonstrated ~~this promised~~ a ~~utility~~ practical purpose and/or a relevant use.

97. The inventors attempted to measure ocular discomfort in cats, conjunctival hyperemia in rabbits, and IOP reduction in monkeys and in themselves and two others, all in single dose experiments. Apotex specifically denies that single dose experiments were capable of demonstrating or forming the factual basis for a sound prediction of any practical purpose and/or relevant use. The inventors did not investigate the compounds in animals or patients suffering from ocular hypertension or glaucoma to determine whether the compounds treat these diseases without causing significant ocular irritation or conjunctival hyperemia in humans (*i.e.*, substantial side effects). The inventors did not investigate the compounds on chronic administration. The

only potential practical purpose and/or potential relevant use is administration on a chronic basis for the treatment of glaucoma or ocular hypertension without causing substantial side effects, and there was no demonstration or sound prediction of that practical purpose and/or relevant use before the filing date of the 132 Patent.

98. Apotex further states that, if anything, the ~~promised~~ utility ~~of 132 Patent~~ was based on a prediction. However, for the reasons cited below, such prediction was not sound.

99. With respect to the animal studies, there are significant differences between the human eye and those of the cats, rabbits and monkeys tested. These differences preclude the extrapolation of the results obtained to humans suffering from glaucoma ~~of~~ or ocular hypertension.

100. Further, the single dose used in each of the animal and the human studies precludes the possibility of a sound prediction. As noted, ocular hypertension and glaucoma are chronic diseases. Prostaglandin drugs, such as latanoprost, are meant for repeated and prolonged use. The single dose study in the 132 Patent does not provide any information as to the effects of latanoprost after repeated use.

101. Moreover, prolonged use increases the occurrence of side effects, and even if discomfort was mild to start, significant discomfort may nonetheless accompany prolonged use.

102. The ability to predict from the inventors' investigations is also limited by the small number of and identity of the subjects tested. The small sample size would not allow a skilled

person to appreciate any significance for the results. A skilled addressee would not extrapolate the results from 3 or 4 healthy test subjects to the glaucoma population in general. In addition, observations were only made at 4, 6 and 8 hours following administration, and there was no observation at the initial phase. This lack of assessment would miss any initial hypertensive phase or side effect occurring at this stage.

103. In addition, the 132 Patent provides very little information about the experiments themselves, preventing the skilled person from meaningfully assessing their predictive value. The protocol for the evaluation of the animals and/or humans was not provided and there is a lack of critical information on parameters that may influence the data and results obtained such as the age, gender, and breed of the animals; the number of subjects tested; mode of application; the time after administration the observations were recorded; the time of onset and duration of the ocular discomfort or conjunctival hyperemia; whether the same cat(s) or rabbits were used for the different $PGF_{2\alpha}$ derivatives, and if so, what wash-out period was used; how the animals were handled during the testing; whether sedation or anaesthesia was employed; the number of handlers and observers involved; the efforts to standardize the assessments; the method and number of IOP readings that were taken at each time point; and the baseline IOP values.

104. Without this information, a skilled addressee would not be able to determine the significance or applicability of the resultant data.

105. Further, the inventors' cat studies were incapable of providing meaningful data. The "signs" of discomfort in cats are uncertain and practically impossible to accurately evaluate.

This is particularly so with respect to the middle scores where there may have been discomfort that was present but not accompanied by "signs" of discomfort as such. It is also unknown whether one or both eyes were tested in each animal and whether there existed any ocular discomfort that occurred after the period of observation.

106. The 132 Patent indicates that the sign of maximal irritation is complete lid closure, but this metric establishes only the minimum threshold for lid closure, not toxicity nor the maximal irritation. No standard or placebo was used and the studies were not blinded to remove evaluator bias. Other, less subjective tests were known and available to evaluate ocular irritation. In sum, because of their deficiencies, the skilled addressee would not view the cat study results as indicative of the discomfort occasioned by the administration of the test compounds, including latanoprost.

107. Similar deficiencies pertain to the ocular hyperemia studies on rabbits. The hyperemia data was collected from photographs of the superior rectus muscle of the rabbit eye, a location having no direct relevance to the human eye. The evaluation of hyperemia also depends on the evaluation of eye colour, which evaluation is based on the review of photographs; however, the skilled person would not know whether the photographs were taken in a standardized manner. No mention is made of what time after administration the observations were made, and the skilled person would recognize that the evaluators may have missed a period of hyperemia.

108. Further, there is no indication that the inventors allowed for biological variation among the individual animals observed. Biological variation is a well-known phenomenon and allows for diverse manifestations of "normal." Given the subjective nature of the tests and the responses, information as to the biological variation is essential to an interpretation of the data obtained.

109. Side effects increase with increasing dose. The dose of latanoprost administered in Table VI was only 1 µg, a dose below the maximum effective concentration. Other dosages used in the studies were random and generally below the concentrations needed to produce the IOP-lowering effects in humans. In some instances, the doses used were unclear, making it impossible for the skilled person to draw any conclusions as to the side effects of a drug.

110. All of the compounds should have been tested at the same dose to get comparative information about the degree of ocular irritation and hyperemia. However, a lower test dose was chosen for some compounds. It seems that, rather than testing the compounds at the effective doses for side effects, the dosage amount was chosen so as to not show side effects. In addition, a skilled person would expect ~~that~~ each drug to be tested at different drug concentrations, but this was not done for the 132 Patent. In all, the skilled person would recognize that the 132 Patent failed to indicate whether ocular irritation would have been observed at the "effective" doses.

111. Accordingly, the inventors had not determined and had no sound basis to predict that the chronic use of latanoprost would not cause ocular irritation, irritation of the corneal

nerves or conjunctive hyperemia in patients with glaucoma or ocular hypertension. Pfizer's product monograph itself concedes that XALATAN patients do suffer from ocular irritation and conjunctive hyperemia.

112. Apotex states that, as of the filing date of the 132 Patent, there was no basis for predicting that all derivatives of PGA, PGB, PGD, PGE or PGF, characterized only by ring substitution in the omega chain were capable of lowering IOP. In fact PGB and PGD were never addressed in the 132 Patent. Further, the patentee admits that some of the compounds forming part of the invention are not useful ~~and do not fulfill the promise of the 132 Patent~~. See page 6 of the 132 Patent.

113. There was, consequently, no basis for predicting that all said derivatives were capable of displaying substantially no ocular irritation while retaining an IOP-lowering effect. Although claims are made for "derivatives of" prostaglandins A, B, D, E and F, wherein the omega chain is modified to include a ring, and being capable of lowering IOP and displaying substantially no ocular irritation, only a limited number of prostaglandin derivatives having omega chains comprising a ring were provided by the disclosure of the 132 Patent. Apotex asserts that insufficient disclosure and insufficient examples had been provided to support the scope of the claims in the 132 Patent given the disclosure of the 132 Patent and thus there is no basis for a sound prediction <u>of any practical purpose and/or relevant use</u>.

114. Furthermore, Apotex states that, as of the filing date of the 132 Patent there was no sound basis for predicting that all derivatives of PGA, PGB, PGD, PGE or PGF, characterized

only by ring substitution in the omega chain had no side effects. In fact, the common knowledge of the person skilled in the art teaches to the contrary.

115. Further, there is no sound basis upon which the named inventors could have predicted that use of said derivatives of the prostaglandins specified were actually useful for treatment of glaucoma. Data presented from experiments conducted with rabbits, cats, monkeys, and healthy subjects does not provide a sound basis to predict ~~the~~ utility ~~of the compounds and uses claimed~~ with respect to treatment of glaucoma and ocular hypertension with reduced side effects in human patients suffering from glaucoma~~, the "promise" of the claimed invention of the 132 Patent~~.

116. In the absence of an actual demonstration of the use of each of the derivatives of prostaglandins of the A, B, D, E and F type as purported in the 132 Patent, there was no sound basis upon which the named inventors could have predicted that use of all of these derivatives of prostaglandin specified in the claims were actually useful for treatment of glaucoma and/or ocular hypertension with reduced side effects in human patients. Data presented from experiments conducted with healthy subjects does not provide a sound basis to predict the utility of these prostaglandin compositions and uses for the treatment of glaucoma and ocular hypertension in patients suffering from glaucoma.

~~117. In addition to the foregoing grounds and without derogating therefrom, Apotex states that the 132 Patent is and always has been invalid, void and of no force and effect for the reasons set out in the Federal Court of Appeal's decision in A-206-10 reported at 2011 FCA 236.~~

118. More particularly, Apotex states that the 132 Patent is and always has been invalid for essentially the following reasons, taken from the Federal Court of Appeal's decision (in A-206-10 reported at 2011 FCA 236) and stated by Apotex to be true and relevant for the purposes of the within action.

(a) The 132 Patent addresses certain prostaglandin derivatives and their use in the treatment of glaucoma or ocular hypertension;

(b) Prostaglandins are naturally occurring substances found in human and animal tissues. $PGF_{2\alpha}$, is a type of prostaglandin that can be esterified into $PGF_{2\alpha}$-isopropyl ester;

(c) Latanoprost, the compound claimed in the 132 Patent, is a prostaglandin derivative that has the following chemical formula: 13,14-dihydro-17-phenyl-18,19,20-trinor $PGF_{2\alpha}$-isopropyl ester;

(d) The eye is a closed sphere that produces a clear fluid called aqueous humor. This fluid is essential to the functioning of the eye as it not only conveys nutrients to it, but also removes from it waste products and contaminants. The drainage of aqueous humor assists in avoiding an increase in intraocular pressure, thus reducing the risk factor for disorders of the eye, including glaucoma and ocular hypertension;

(e) Ocular hypertension describes an intraocular hypertension without damage to the optic nerve. Glaucoma describes a group of disorders characterized by damage to the optic nerve that results in loss of vision if the condition is left untreated. There is no cure for glaucoma but it, as well as ocular hypertension, can be managed by reducing intraocular pressure. This is achieved by use of drugs in one of two ways: reduction in the production of aqueous humor; or, with latanoprost, increase in the outflow of aqueous humor;

(f) A high level of compliance is needed by patients treating their glaucoma with drugs. Therapies with less frequent doses are preferred because they contribute to patients' compliance, as does the tolerability of the drugs used. The tolerability of the drug is usually measured in terms of side effects, which may be systemic (occurring throughout the body) or localized (around the eye);

(g) Prior to the advent of latanoprost, other drugs were available for the treatment of glaucoma and ocular hypertension. They, however, caused undesirable effects, ranging from tingling and hyperaemia to emphysema and death. Latanoprost was claimed to "reduce intraocular pressure without causing substantial ocular irritation" (claim 1 of the 132 Patent);

(h) At the time of filing of the application for the 132 Patent, the person of ordinary skill in the art ("POSITA") would have understood glaucoma to be a chronic condition that required chronic treatment;

~~(i) The promise of the 132 Patent, broadly stated, is the chronic use of a compound (latanoprost) for the effective treatment of a chronic medical condition (glaucoma);~~

~~(j) More specifically, the promised utility of the 132 Patent is that latanoprost, when administered on a chronic basis, reduces intraocular pressure without causing substantial side effects;~~

~~(k) Stated alternatively, the promise of the patent is to treat glaucoma and intraocular hypertension on a chronic basis without causing substantial side effects;~~

(l) ~~However, a~~ At the time of filing, the inventors had only conducted "single dose" studies on animals and healthy humans and latanoprost had not been tested on patients with glaucoma or on a chronic basis;

(m) At the time of filing, ~~the~~ a utility ~~of the patent~~ was not demonstrated;

(n) If anything, the 132 Patent was based on a prediction of utility, i.e., that which was observed in the single dose study could soundly be predicted to apply to chronic use;

(o) However, any such prediction was not a "sound prediction" under Canadian patent law;~~.~~

(p) The inventors of the 132 Patent had no factual underpinning for any prediction that a single dose study could be applied to chronic use or for any other prediction;

(q) The studies conducted by the inventors consisted of putting a single dose of the compounds in the eye of the animal and human models. The tests were broken down so that the efficacy of the compounds was tested in monkeys and humans, whereas toxicity (irritation and hyperaemia) was tested in rabbit and cat models;

(r) However, none of these studies were chronic use studies as none of them used multiple doses;

(s) Because the inventors had no factual underpinnings for any prediction, they had no articulable and "sound" line of reasoning from which to infer their ~~promised~~ result;

(t) Moreover, any line of reasoning that the inventors might have had is nowhere to be found in the disclosure of the 132 Patent; and

(u) Accordingly, the 132 Patent is invalid for want of a sound prediction.

118A. Claim 12 (which claims a therapeutic ophthalmological composition containing latanoprost for the treatment of glaucoma or ocular hypertension in an amount sufficient to reduce intraocular pressure without causing substantial ocular irritation) is invalid because there was no demonstration or sound prediction by the filing date that the subject matter of

claim 12 could be used (i) for the treatment of glaucoma or ocular hypertension in an amount sufficient to reduce intraocular pressure without causing substantial ocular irritation; and/or (ii) for any practical purpose and/or relevant use.

118B. Claim 19 (which claims latanoprost) is invalid because there was no demonstration or sound prediction by the filing date that the subject matter of claim 19 could be used (i) for the treatment of glaucoma or ocular hypertension in an amount sufficient to reduce intraocular pressure without causing substantial ocular irritation; and/or (ii) for any practical purpose and/or relevant use. Should Pfizer assert a use for the subject matter of claim 19 other than the treatment of glaucoma or ocular hypertension in an amount sufficient to reduce intraocular pressure without causing substantial ocular irritation, then the use asserted by Pfizer does not amount to a practical purpose or an actual relevant use such that no demonstration or sound prediction was possible for the subject matter of claim 19 as of the filing date. As admitted by the 132 Patent, there can be no practical usefulness for prostaglandins that merely lower intraocular pressure without being capable of treating glaucoma or ocular hypertension.

118C. Claim 31 (which claims the use of latanoprost in the treatment of glaucoma or ocular hypertension) is invalid because there was no demonstration or sound prediction by the filing date that the subject matter of claim 31 could be used (i) for the treatment of glaucoma or ocular hypertension in an amount sufficient to reduce intraocular pressure without causing substantial ocular irritation; and/or (ii) for any practical purpose and/or relevant use. Should Pfizer assert a use for the subject matter of claim 31 other than the treatment of glaucoma or

ocular hypertension in an amount sufficient to reduce intraocular pressure without causing substantial ocular irritation, then that use does not amount to a practical purpose or an actual relevant use such that no demonstration or sound prediction was possible for the subject matter of claim 31 as of the filing date. As admitted by the 132 Patent, there can be no practical usefulness for prostaglandins that merely lower intraocular pressure without being capable of treating glaucoma or ocular hypertension.

118D. Claim 38 (which claims the use of latanoprost in the treatment of glaucoma or ocular hypertension) is invalid for lack of demonstrated utility or sound prediction of utility by the filing date for the same reasons as claim 31.

^

f. Claims Broader than the Invention

128. The 132 Patent purports to cover a particularly wide range of compounds, namely derivatives of prostaglandins A, B, D, E and F, wherein the omega chain is modified to include a ring structure. All of these derivatives are generally specified and claimed to lower IOP without causing substantial ocular irritation. This combination of desirable properties functions as a qualifying characteristic of compounds of the purported invention of the 132 Patent.

129. The compounds evaluated ~~to complete this promise~~ are set out at page 6 of the 132 Patent, as summarized in the Table therein. These are:

(a) 16-phenyl-17,18,19,20-tetranor-$PGF_{2\alpha}$-isopropylester;

(b) 17-phenyl-18,19,20-trinor- $PGF_{2\alpha}$-isopropylester;

(c) 15-dehydro-17-phenyl-18,19,20-trinor- $PGF_{2\alpha}$-isopropylester;

(d) 16-phenoxy-17,18,19,20-tranor- $PGF_{2\alpha}$-isopropylester;

(e) 17-phenyl-18,19,20-trinor-PGE_2-isopropylester;

(f) 13,14-dihydro-17-phenyl-18,19,20-trinor- PGE_2-isopropylester;

(g) 15-(R)-17 -phenyl-18,19,20-trinor- $PGF_{2\alpha}$-isopropylester;

(h) 16-[4-(methoxy)-phenyl]-17,18,19,20-trinor- $PGF_{2\alpha}$-isopropylester;

(i) 13,14-dihydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-isopropylester;

(j) 18-phenyl-19,20-dinor- $PGF_{2\alpha}$-isopropylester; and

(k) 19-phenyl-20-nor- $PGF_{2\alpha}$-isopropylester.

130. Thus, although claims are made for "derivatives of" prostaglandins A, B, D, E and F, wherein the omega chain is modified to include a ring, and being capable of lowering IOP and displaying substantially no ocular irritation, only a limited number of prostaglandins having omega chains comprising a ring were provided by the disclosure of the 132 Patent. That is to say, insufficient material has been submitted to support the claims in the 132 Patent given the

common knowledge of the person skilled in the art as discussed herein ~~in this NOA~~ and given the statements in the 132 Patent.

131. Thus, no support was ever provided ~~for the claim~~ that prostaglandins of the B or D type, having omega chains comprising a ring structure, were capable of lowering IOP, while displaying substantially no ocular irritation.

132. Thus, of the prostaglandin analogues that were evaluated, only one each of derivatives of PGA and PGE were evaluated, namely, 13,14-dihydro-17-phenyl-18,19,20-trinor-PGA_2-isoproylester and 17-phenyl-18,19,20-trinor-PGE_2-isopropylester.

133. No IOP data was provided in the patent for any PGA or PGE derivative, nor has any IOP data ever been published for 13,14-dihydro-17-phenyl-18,19,20-trinor-PGA_2-isoproylester.

134. The only reference to ever published IOP data for the 17-phenyl-18,19,20-trinor-PGE_2-isopropylester was not available to the public until nearly 8 years later SE9702706A0 – filed July 11, 1997 and published as PCT WO99/02165 on January 21, 1999 (Document 83). However, even that compound is shown by the 132 Patent to have a degree of hyperemia, no different from that of the prior art compound, $PGF_{2\alpha}$-isopropylester, within experimental error (See Table IV, page 26).

135. In light of the relative uncertainty at the time of filing of the 132 Patent, it is clear the claims purport to cover material substantially broader than that (if any at all)

deserving of protection. Further, not all $PGF_{2\alpha}$ derivatives claimed with phenyl rings on the omega chain have no irritation as admitted by the patentee.

136. ~~In spite of the alleged utility of said prostaglandin derivatives, t~~The 132 Patent admits at page 7, line 8:

> The invention thus relates to the use of certain derivatives of PGA, PGB, PGD, PGE and PGF for the treatment of glaucoma or ocular hypertension. Among these derivatives defined above it has been found that some are irritating or otherwise not optimal, and in certain cases not even useful due to adverse effects and these are excluded in that the group of prostaglandin derivatives defined above is limited to therapeutically effective and physiologically acceptable derivatives. So is for instance (1) 16-phenyl-17,18,19,20-tetranor-$PGF_{2\alpha}$-isopropyl ester irritating while this can be eliminated by substituting the phenyl ring with a methoxy group giving formula (8) which represent a therapeutically more useful compound.

136A. As described above, the 132 Patent asserts that latanoprost can be chronically administered for the treatment of glaucoma or ocular hypertension without causing substantial ocular irritation. However, for the reasons described under the headings "Lack of Utility" and "No Demonstrated Utility / Lack of Sound Prediction", there was no demonstration or sound prediction of this before the filing date of the 132 Patent and this was never achieved. This constitutes the mischief of overpromising and renders all of the Asserted Claims invalid for overbreadth:

(a) claim 12 (which claims a therapeutic ophthalmological composition containing latanoprost for the treatment of glaucoma or ocular hypertension in an amount sufficient to reduce intraocular pressure without causing substantial ocular

irritation) is invalid for overbreadth because glaucoma and ocular hypertension are chronic disorders that require chronic administration of a medicament for treatment and this is more than what the named inventors of the 132 Patent had invented because they had not demonstrated or soundly predicted that the subject matter of claim 12 would not cause substantial ocular irritation upon the chronic administration required for the treatment of glaucoma or ocular hypertension. The 132 Patent improperly asserts that the claimed composition can be usefully administered on a chronic basis for the treatment of glaucoma or ocular hypertension without causing substantial side effects;

(b) claim 19 (which claims latanoprost) is invalid for overbreadth because the 132 Patent asserts that latanoprost can be usefully administered on a chronic basis for the treatment of glaucoma or ocular hypertension without causing substantial side effects and this is more than what the named inventors of the 132 Patent had invented because they had not demonstrated or soundly predicted that latanoprost would not cause substantial ocular irritation and/or conjunctival hyperemia upon the chronic administration required for the treatment of glaucoma or ocular hypertension. A compound that has not been demonstrated or soundly predicted to avoid these substantial side effects upon chronic administration cannot be useful in the treatment of glaucoma or ocular hypertension. Further, while the 132 Patent asserts that its invention is limited in scope to compounds that can be usefully administered on a chronic basis for

the treatment of glaucoma or ocular hypertension without causing substantial side effects, claim 19 claims a compound without limitation as to its properties and thus is necessarily overly broad relative to the invention made or disclosed;

(c) claim 31 (which claims the use of latanoprost in the treatment of glaucoma or ocular hypertension) is invalid for overbreadth because glaucoma and ocular hypertension are chronic disorders that require chronic administration of a medicament for treatment and this is more than what the named inventors of the 132 Patent had invented because they had not demonstrated or soundly predicted that latanoprost would be useful upon the chronic administration required for the treatment of glaucoma or ocular hypertension. Further, a compound that has not been demonstrated or soundly predicted to avoid substantial side effects upon chronic administration cannot be useful in the treatment of glaucoma or ocular hypertension. The 132 Patent improperly asserts that latanoprost can be usefully administered on a chronic basis for the treatment of glaucoma or ocular hypertension without causing substantial side effects;

(d) claim 38 (which claims the use of latanoprost in the treatment of glaucoma or ocular hypertension) is invalid for overbreadth for the same reasons as claim 31.

137. All the claims of the 132 Patent are invalid, void and of no effect as being broader than any invention made or disclosed therein.

g. Insufficient Disclosure

138. Apotex alleges that each of the claims of the 132 Patent is invalid, void and of no effect on the basis that the specification does not comply with subsection 27(3) of the *Patent Act* (and/or section 36 of the *Patent Act* as it existed before 1989) since it does not correctly and fully describe the invention and its operation or use as contemplated by the inventors. Apotex alleges that the specification is insufficient because it does not fully define in clear terms the nature and characteristics of the special attributes or substantial advantages, if any, that are alleged to be possessed by the claimed compounds having regard to the provisions of the *Patent Act*.

139. Apotex alleges that the specification of the 132 Patent fails to correctly and fully describe the purported invention as claimed in each of the claims in issue and the use of such alleged invention.

140. Apotex also alleges that the purported inventors of the 132 Patent did not disclose everything that is essential in order to enable one of ordinary skill in the art to determine which, if any, of the thousands of possible compounds included within the claims of the 132 Patent would work or for which there was a sound prediction.

141. The specification of the 132 Patent discloses that the inventors have discovered new and inventive prostaglandin derivatives for lowering IOP while simultaneously substantially eliminating the ocular irritation expected from the prior art compounds. In describing

preferred derivatives of the invention, the specification of the 132 Patent states at page 6, line 14:

> The most preferred derivatives at present are those in which the omega chain of the prostaglandin has the 18,19,20-trinor form, and especially the 17-phenyl analogs, such as the 15-(R)-, 15-dehydro and 13,14-dihydro-17-phenyl-18,19,20-trinor forms. Such derivatives are represented by (3), (6), (7) and (9) in the formulas given in Table 1.
>
> In the formula given above the most preferred structure at present is accordingly obtained when the prostaglandin is a derivative of PGA, PGD, PGE or PGF, especially of PGA2, PGD2, PGE2 and PGF2α
>
> B is a single bond or a double bond.
>
> D is a carbon chain with 2-5, especially 3 atoms; 15 having a carbonyl or (S)-OH substituent and C16-19 having lower alkyl substituents, or preferably H.
>
> R_2 is a phenyl ring optionally having substituents selected among alkyl and alkoxy groups.
>
> The invention thus relates to the use of certain derivatives of PGA, PGB, PGD, PGE and PGF for the treatment of glaucoma or ocular hypertension. Among these derivatives defined above it has been found that some are irritating or otherwise not optimal, and in certain cases not even useful due to adverse effects and these are excluded in that the group of prostaglandin derivatives defined above is limited to therapeutically effective and physiologically acceptable derivatives. So is for instance (1) 16-phenyl-17,18,19,20-tetranor-PGF2α-isopropyl ester irritating while this can be eliminated by substituting the phenyl ring with a methoxy group giving formula (8) which represents a therapeutically more useful compound. (emphasis added)

142. But these admittedly inoperable derivatives set out above were never omitted and thus disclaimed by the patentee of the 132 Patent.

143. Thus, the 132 Patent teaches that certain derivatives included within the "preferred derivatives" fail ~~to fulfill the promise of the patent~~ due to adverse effects, and are therefore to be excluded from the claims (even though, in fact, they continue to be included).

No further statements are provided as to the identification of these and other compounds ~~that do not fulfill the promise of the 132 Patent~~, other than the broad blanket statement that they are excluded, and the claimed derivatives are allegedly limited only to the group of prostaglandin derivatives having therapeutic efficacy and physiological acceptability. But these inoperative derivatives otherwise remain included in the claims. No qualifying characteristic is further provided in each claim such that said "inoperative" derivatives may be identified or eliminated. In fact, the only guidance to one of ordinary skill in the art is the very general statement that a particularly preferred derivative has inappropriate irritating side effects which are eliminated upon substitution by a methoxy group.

144. Even if guidance had been provided (which is denied) as to identification of those compounds having no particular utility so as to separate those derivatives from those suitable derivatives having an IOP lowering ocular irritative effect, the specification of the 132 Patent would still be insufficient.

145. Apotex therefore, alleges that each of the claims of the 132 Patent is invalid, void and of no effect on the basis that the specification does not comply with section 27(3) of the *Patent Act* (and/or section 36 of the *Patent Act* as it existed before 1989) since it does not correctly and fully describe the invention and its operation or use as contemplated by the inventors. Apotex further alleges that the specification is insufficient because it does not fully define in clear terms the nature and characteristics of the special compounds and their special attributes or substantial advantages, if any, that are alleged to be possessed by each of the claimed compounds or included in the composition and use claims.

145A. Because the 132 Patent over-promises, it contains a disclosure that is not correct and full and it states an unsubstantiated use or operation of the purported invention, which constitutes a failure to fulfill the requirements of subsection 27(3) of the *Patent Act* (and/or section 36 of the *Patent Act* as it existed before 1989), thereby rendering the 132 Patent and all of the Asserted Claims invalid.

145B. As described above, the 132 Patent asserts that latanoprost can be usefully administered on a chronic basis for the treatment of glaucoma or ocular hypertension without causing substantial side effects. However, for the reasons described under the headings "Lack of Utility" and "No Demonstrated Utility / Lack of Sound Prediction", there was no demonstration or sound prediction of this before the filing date of the 132 Patent and this was never in fact achieved. The 132 Patent thus asserts an unsubstantiated use or operation for the invention, which constitutes the mischief of overpromising and renders all of the Asserted Claims invalid for failure to fulfill the requirements of subsection 27(3) of the *Patent Act* (and/or section 36 of the *Patent Act* as it existed before 1989).

h. Place of Trial

146. As proposed in the claim, Apotex proposes that the trial of the action, including the counterclaim, take place at Ontario, Canada.

^^September 15, 2017

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Schedule "A"

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Court File No. T-1064-13

FEDERAL COURT

B E T W E E N:

APOTEX INC.

Plaintiff
(Defendant by Counterclaim)

- and -

PFIZER CANADA INC.

Defendant
(Plaintiff by Counterclaim)

- and -

PHARMACIA AKTIEBOLAG

Plaintiff by Counterclaim

FURTHER AMENDED REPLY AND DEFENCE TO COUNTERCLAIM
(dated September 15, 2017)

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FEDERAL COURT

SOLICITORS OF RECORD

DOCKET:	T-1064-13
STYLE OF CAUSE:	APOTEX INC. v PFIZER CANADA INC. ET AL
PLACE OF HEARING:	VANCOUVER, BRITISH COLUMBIA
DATE OF HEARING:	OCTOBER 16, 2017
ORDER AND REASONS:	MANSON J.
DATED:	OCTOBER 25, 2017

APPEARANCES:

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Jordana Sanft Tracey Stott	FOR THE DEFENDANT / PLAINTIFF BY COUNTERCLAIM

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