Date: 20061207
Docket: T-560-05
Citation: 2006 FC 1471

OTTAWA, ONTARIO, December 7, 2006
PRESENT: The Honourable Mr. Justice von Finckenstein

BETWEEN:

PFIZER CANADA INC.
and WARNER-LAMBERT COMPANY, LLC

Applicants

and

THE MINISTER OF HEALTH
and NOVOPHARM LIMITED

Respondents

REASONS FOR ORDER AND ORDER

[1] This is an application pursuant to s. 6(1) of the *Patented Medicines (Notice of Compliance) Regulations*, 1993, SOR/93-133 ("NOC Regulations"), for an Order prohibiting the Minister of Health (the "Minister") from issuing a Notice of Compliance ("NOC") under the *Food and Drug Regulations*, C.R.C. c. 870, to the Respondent, Novopharm Limited ("Novopharm"), with respect to atorvastatin calcium, 10 mg, 20 mg, 40 mg, or 80 mg strength tablets until after the expiration of Canadian Patent 2,021,546 (the "546 Patent").

Procedural Background

[2] The Applicants, Pfizer Canada Inc. and Warner-Lambert Company, LLC (collectively, "Pfizer"), manufacture and sell an anti-cholesterol drug under the trade name LIPITOR, which is contained in the 546 Patent. The active ingredient of LIPITOR is the atorvastatin calcium, a salt.

[3] The 546 Patent was filed with the Canadian Patent Office on July 19, 1990, and published on January 22, 1991. It is based on a priority filing of U.S. Patent 384,187 filed on July 21, 1989, but which has since been abandoned and is now continued under U.S. Patent 5,273,995. Accordingly, the patent is governed by the *Patent Act*, R.S.C. 1985, c. P-4 and the relevant date upon which the patent will be interpreted is the date of publication, i.e., January 22, 1991. (*Whirlpool Inc. v. Camco Inc.*, 2000 SCC 67 (CanLII), [2000] 2 S.C.R. 1067 at para. 56).

[4] The 546 Patent was issued to Warner-Lambert Company, a predecessor of the Applicant Warner-Lambert Company, LLC on April 29, 1997, and it expires on July 19, 2010. The only claim in dispute is claim 6.

[5] Novopharm is seeking an NOC to allow it to produce a generic version of atorvastatin calcium. In making its application, Novopharm sent a Notice of Allegation ("NOA") in a letter dated February 3, 2005, to Pfizer comparing its drug to LIPITOR and referencing the 546 Patent.

The NOA alleges that the 546 Patent is invalid for three reasons: anticipation, obviousness, and double patenting. The relevant portions of the NOA are attached hereto as Annex 1.

[6] Pfizer disputes these allegations and brought this application seeking an order prohibiting the Minister from issuing an NOC to Novopharm prior to the expiration of the 546 Patent.

Chemical Background - Underlying Concepts

[7] In order to provide a context to the discussion that follows, I will briefly describe the underlying concepts and what the invention involves.

[8] First, cholesterol is synthesized in most body tissues and is necessary for normal body functions. Cholesterol is carried throughout the body on two types of particles: low density lipoproteins (LDL) and high density lipoproteins (HDL).

[9] Cholesterol biosynthesis is the process of producing cholesterol in the body. Cholesterol is synthesized through a biochemical pathway made up of a number of steps (between 20-40).

[10] Many different enzymes (proteins that control biochemical reactions) are involved in cholesterol biosynthesis. One of the early steps in the cholesterol biosynthesis pathway involves an enzyme called HMG-CoA reductase. This step is often called the "rate limiting step" in the pathway.

[11] Drugs that prevent HMG-CoA reductase from performing its functions in the cholesterol biosynthesis pathway are called HMG-Co-A reductase inhibitors. By inhibiting cholesterol biosynthesis, these drugs decrease the production of cholesterol.

[12] Statins are drugs which function as HMG-CoA reductase inhibitors. There are two kinds of statins: those derived from natural products (i.e., natural statins) and those produced synthetically (i.e., synthetic statins). Natural statins are derived from fungal fermentation. Synthetic compounds are produced by medicinal chemists. LIPITOR is a member of a class of synthetic statins.

[13] Pfizer made the following statements regarding LIPITOR:

> LIPITOR® is a blockbuster, but not in the traditional sense: it was not the first drug in its class. Rather, it was the *fifth* in the commercial statin marketplace. However, it is one of a kind and the first of its kind: it is a novel compound; it is the first statin to be formulated as a calcium salt (all previous statins were formulated as sodium salts); it is the first synthetic statin to be marketed in a form other than as a racemate.
>
> LIPITOR® has become a commercial success because of the advantageous properties of atorvastatin calcium. It has dominated the market: it has become the first drug ever to reach over a billion dollars in sales in its first year, is currently the largest selling drug in every country in which it is sold, and is the largest selling drug of all time.

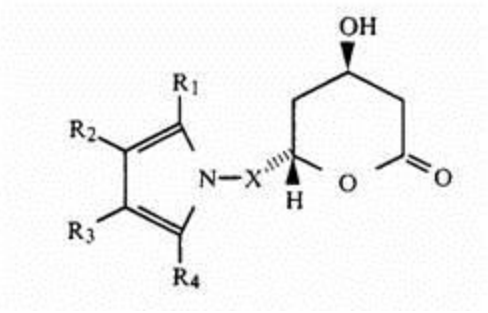
> Not surprisingly, Novopharm wants to take as large a share of the valuable LIPITOR® market as it can by selling its own atorvastatin calcium, a generic copy. To do so, it must invalidate the single patent claim, claim 6, to the most successful salt in pharmaceutical history.
>
> (A.R. Vol. 29 at 9940.)

Prior Patents

[14] The 546 Patent is based on the prior art of U.S. Patent 4,681,893 ("893 Patent"). The 893 Patent was filed with the U.S. Patent Office on May 30, 1986, and issued on July 21, 1987. It describes a class of statins, including natural statins which were commercialized as lactones and compounds. The 893 Patent includes individual enantiomers and mixtures, including racemic mixtures.

[15] "Enantiomers" are a pair of isomers that are non-superimposable mirror images of one another. The most common analogy for enantiomers is a pair of hands. "Racemate", also known as a "racemic mixture", is a 50/50 mixture of enantiomers.

[16] The invention of the 893 Patent provided for compounds with the structural formula:



Wherein X is $–CH_2—$, $--CH_2CH_2—$, $--CH_2CH_2CH_2—$ or $–CH_2CH(CH_3)—$

[17] It also provides a list of substituents for R_1 to R_4, including substituents making up the atorvastatin racemate.

[18] Thus, the 893 Patent describes a broad class of compounds including the 4-hydroxypyran-2-ones and the corresponding ring-opened acids, and the pharmaceutically acceptable salts thereof.

[19] These compounds are in practice used in its salt form. The salt most commonly used was the sodium salt, although any number of salts may be used. In describing what "pharmaceutically acceptable metal salt" meant, the 893 Patent includes the following salts: sodium, potassium, calcium, magnesium, aluminium, iron, and zinc ions, but it did not draw special attention to the calcium salt specifically.

[20] The 893 Patent gave a detailed description of the racemic mixture by stating [emphasis added]:

> This asymmetry gives rise to four possible isomers, two of which are the R-cis and S-cis-isomers and the other two of which are the R-trans and S-trans-isomers. This invention contemplates only the trans- form of the compounds of formula I above.

[21] "Cis" and "Trans" are terms which imply relative stereochemistry. Cis means that two chemical groups in a molecule are on the same side of a plane, but it does not tell you which side of the plane the groups are on. Trans means that two chemical groups in a molecule are on opposite sides of a plane.

[22] This might be a good point to say a few words about the nomenclature of this case to clear up any possible confusion. The compound from which the enantiomers are resolved has no name of its own. It is called the atorvastatin racemate or atorvastatin racemic mixture. The R- trans enantiomer of the atorvastatin racemate is called the atorvastatin. The S- trans enantiomer has no name of its own and is always referred to as the S-trans enantiomer. LIPITOR contains the calcium salt of atorvastatin (the R-trans enantiomer).

[23] The 893 Patent corresponds to the Canadian Patent 1,268,768 ("768 Patent"). The 768 Patent was filed on May 7, 1987, and issued on May 8, 1990.

[24] Approximately three years after the 893 Patent was filed, the Applicants filed another patent, this time a process patent with the Canadian Patent Office on February 7, 1989. This was the Canadian Patent 1,330,441 ("441 Patent").

[25] The 441 Patent discloses and claims chemical processes that can be used to make chemical compounds. This includes processes used in the production of atorvastatin.

Issue

[26] Are Novopharm's allegations (that the 546 patent is invalid on the basis of anticipation, obviousness and double patenting) justified?

Applicable Jurisprudence

[27] The jurisprudence regarding NOCs is extensive. It is best set out by Stone J.A. in *Hoffman-La Roche Ltd. v. Canada (Minister of National Health & Welfare)* (1996), 205 N.R. 331 at para. 8, 70 C.P.R. (3d) 206 (F.C.A.):

> It seems to me that the core guidance of these decisions, insofar as it is applicable to the case at bar, may be summarized as follows:
>
> > 1. Applications made pursuant to subsection 6(1) of the Regulations are governed by the procedural rules contained in Part V.1 of the *Federal Court Rules*, [C.R.C. 1978, c. 663] - "*Applications for Judicial Review*". *Bayer AG*, supra, per Mahoney J.A., at page 336 [C.P.R.];
> >
> > 2. The initiator of a section 6 proceeding, being the person having the carriage of the litigation, bears "the initial burden of proof" which is a difficult burden because "it must be to

disprove some or all of the allegations in the notice of allegation which, if left unchallenged, would have allowed the Minister to issue a notice of compliance". *Merck Frosst*, supra, per Hugessen J.A., at page 319 [C.P.R.];

3. This burden, known in a civil case as either the "persuasive burden" or the "legal burden", is the burden of establishing a case to the civil standard of proof. By contrast, the "evidential burden" consists of the burden of putting an issue in play and means that a party has the responsibility to ensure that there is sufficient evidence of the existence or non-existence of a fact or an issue on the record to pass the threshold for that particular fact or issue. *Nu-Pharm*, supra, per Stone J.A., at page 197 [N.R.].

4. Where the notice of compliance of a second person alleges non-infringement, the court should start from the proposition that "the allegations of fact in the notice of allegation are true except to the extent that the contrary has been shown by the applicant". *Merck Frosst*, supra, per Hugessen J.A., at page 319 [C.P.R.];

5. In determining whether or not the allegations are "justified" "the court must then decide whether, on the basis of such facts as have been assumed or proven, the allegations would give rise in law to the conclusion that the patent would not be infringed by the respondent". *Merck Frosst*, supra, per Hugessen J.A., at page 319 [C.P.R.];

6. The Minister's decision of whether to issue a notice of compliance must turn on whether the allegations of the second person are "sufficiently substantiated to support a conclusion for administrative purposes ... that the applicant's patent would not be infringed if the generic's product is put on the market". *Pharmacia*, (A-332-94) supra, per Strayer J.A., at page 216 [C.P.R.];

7. Where second persons fail to file notices of allegation or adequate notices of allegation they "must assume their own risk when it comes to attacks on the adequacy of such allegations once prohibition proceedings are commenced". Bayer AG, (A-669-93) supra, per Strayer J.A., at page 134 [C.P.R.].

8. The requirement in s. 5(3)(a) of the *Regulations* that a second person provide a detailed statement "seems intended ... [to make] the patentee ... fully aware of the grounds on which the applicant seeks issuance of a NOC [that will not lead to infringement of the patent] before the patentee decides whether or not to apply to a court for a determination. Such disclosure would define the issues at a very early stage." *Bayer*

> *AG*, (A-389-93) supra, per Mahoney J.A., at pages 337-338 [C.P.R.];
> 9. A bald statement of non-infringement in a detailed statement without any factual assertion in support thereof does not meet the requirements of s. 5(1)(b)(iv) of the *Regulations*. *Nu-Pharm*, supra, per Stone J.A., at page 199 [N.R.];
> 10. A common law presumption that a second person's process would infringe the patent applies where: that person has asserted no facts to support his allegation of non-infringement; the evidence of non-infringement lay peculiarly within his knowledge; no evidence of non-infringement has been presented by that person; and the first person has no other available means of accessing such evidence. *Nu-Pharm*, supra, per Stone J.A., at page 200 [N.R.].

Burden of Proof

[28] Pfizer in its factum states at para. 122:

> Facts that are set out in the Notice of Allegation in relation to allegations of invalidity are not presumed to be true. A presumption that facts in a Notice of Allegation are true arises only with respect to allegations of non-infringement. The only allegations in this case are allegations of invalidity. As a result, no facts set out in Novopharm's Notice of Allegation are presumed to be true.
>
> (A.R. Vol. 29 at 9972.)

[29] This is not a correct reflection of the law on this point. The issue of the interaction of s. 43(2) of the *Patent Act* and the NOC Regulations has been dealt with on numerous occasions by this Court (see *Pfizer Canada Inc. v. Apotex Inc.*, 2002 FCT 1138, (2002), 22 C.P.R. (4th) 466 at paras. 82-83, 2002 FCT 1138 (CanLII), 225 F.T.R. 1, Dawson J.; *Abbott Laboratories v. Canada (Minister of Health)*, 2004 FC 1349 (CanLII), (2004), 36 C.P.R. (4th) 437 at paras. 103-106, 260 F.T.R. 276, Gibson J.; aff'd 2005 FCA 250 (CanLII), (2005), 339 N.R. 277; *GlaxoSmithKline Inc. v. Genpharm Inc.*, 2003 FC 1248, (2003), 30 C.P.R. (4th) 360 at para. 45, 2003 FC 1248 (CanLII), 241 F.T.R. 42, Heneghan J.; *Janssen-Ortho Inc. v. Novopharm Ltd.* 2004 FC 1631 (CanLII), (2004), 35 C.P.R. (4th) 353, at paras. 13-21, 264 F.T.R. 202, Mosley J.; *Sanofi-Synthelabo Canada Inc. v. Apotex Inc.*, 2005 FC 390 (CanLII), (2005), 39 C.P.R. (4th) 202 at 209, 271 F.T.R. 159, Shore J.).

[30] All these cases stand for the proposition that the applicant must demonstrate on a balance of probabilities, that the respondent's allegations of non-infringement or invalidity of the patent are not justified. As Shore J. stated in *Sanofi-Synthelabo, supra* at para. 9:

> The applicant has the overall legal burden of proof. Nevertheless, the Respondent, as the entity which has made its allegations in the NOA, has the obligation to put these allegations "in play", i.e. to ensure there is sufficient evidence of these allegations by which to present issues

> for examination (*Eli Lilly & Co. v. Nu-Pharm Inc.* (1996), 69 C.P.R. (3d) 1, [1996] F.C.J. No. 904 (F.C.A.) (QL)).

[31] It is thus the duty of the Court to consider each of the allegations of invalidity, and in view of the evidence submitted by the Respondent, determine whether the evidence submitted was sufficient to rebut the statutory presumption of validity. If the evidence was sufficient, the Court then considers the evidence as a whole to determine whether the Applicant had satisfied its burden of disproving the Respondent's allegation of invalidity.

Findings Required

[32] Given the nature and structure of NOC proceedings, in order to grant the requested prohibition order, the Court must come to the conclusion that Novopharm's allegations are not justified. Conversely, in order to not grant a prohibition order, the Court must make a determination that the patent is invalid.

Experts

[33] Both parties called a host of experts. Attached as Annex 2 is a list of the experts called by each side. The experts differed in their testimony. Particularly, their evidence differs on what a person skilled in the art would have known or assumed. Their evidence will be extremely helpful in dealing with the issues of anticipation and obviousness. These issues however, are ultimately questions for the Court to decide in light of the expert testimonies received. Accordingly, I will treat the expert evidence in the same way as Campbell J. in *AB Hassle v. Apotex Inc.*, 2003 FCT 771 (CanLII), 2003 FCT 771, (2003), 27 C.P.R. (4th) 465 at para. 16:

> 16 Each of the expert witnesses to the present case have sworn that the evidence they have provided is true. On this basis, an evaluator of the evidence must start from the proposition that the witnesses are credible unless good cause is shown, and can be articulated, to the contrary (for an example of this general principle see: *Maldonado v. Canada (Minister of Employment and Immigration)*, [1980] 2 F.C. 302 (C.A.). That is, while they might hold differing views on a given topic, it must be assumed that they are not just saying things to bestow a benefit on the party who is relying on their evidence. In my opinion, it is unfair to the witnesses and, accordingly, to each of the parties, to make negative credibility findings in the guise of findings of weight without seeing and hearing each witness testify.

Patent Construction

[34] Any case involving patents starts with construction of the patent. In *Biovail Pharmaceuticals Inc. v. Canada (Minister of National Health and Welfare)*, 2005 FC 9 (CanLII), (2005), 37 C.P.R. (4th) 487, 267 F.T.R. 243, Harrington J. succinctly summarized the jurisprudence on the rules for patent construction at paragraph 15 which I intend to follow:

It is a pre-requisite to considerations of both patent validity and infringement that the language of what is claimed in the patent be properly considered. The Court can do no better than to take the same approach in an NOC proceeding, keeping in mind the restricted purpose of the proceeding. The Supreme Court has done much to codify and clarify patent claim construction in two recent cases handed down the same day: *Free World Trust v. Electro-Sante Inc.*, 2000 SCC 66 (CanLII), [2000] 2 S.C.R. 1024, 9 C.P.R. (4th) 168 and *Whirlpool Corp. v. Camco Inc.*, 2000 SCC 67 (CanLII), [2000] 2 S.C.R. 1067, 9 C.P.R. (4th) 129. The reasons in both were given by Mr. Justice Binnie. I take the following principles as having particular relevance to this case:

> 1. A patent is construed as a bargain between the inventor and the public. In consideration of disclosing the invention, the inventor is given a temporary monopoly to exploit it.
> 2. It is a statutory requirement that the patent contain a specification and end with a claim or claims "defining distinctly and in explicit terms the subject-matter of the invention for which an exclusive privilege or property is claimed". The specification must be sufficiently full, clear, concise and exact "as to enable any person skilled in the art or science to which it pertains, or to which it is most closely connected, to make, construct, compound or use it". (*Patent Act*, R.S.C. 1985, c. P-4, as amended, s. 27)
> 3. The patent is notionally addressed to a person skilled in the art or science of the subject-matter and is to be read as such a person would have read it when it first became public. (More will be said about this skilled reader.)
> 4. The claims are to be read in an informed and purposive way to permit fairness and predictability and to define the limits of the monopoly "[I]ngenuity of the patent lies not in the identification of the desired result but in teaching one particular means to achieve it. The claims cannot be stretched to allow the patentee to monopolize anything that achieves the desired result" (*Free World Trust*, paras. 31, 32).
> 5. The claim portion of the patent specification takes precedence over the disclosure portion in the sense that the disclosure is read to understand what was meant by a word in the claims "but not to enlarge or contract the scope of the claim as written and thus understood" (*Whirlpool*, para. 52).
> 6. It is only such novel features that the inventor claims to be essential that constitute the "pith and marrow" of the claim. "The key to purposive construction is therefore the identification by the Court with the assistance of the skilled reader, of the particular words or phrases in the claims that

describe what the inventor considered to be the "essential" elements of his invention" (*Whirlpool*, para. 45).

7. Some elements of the claimed invention are essential and others are not, based either on common knowledge when the patent was published or according to the intent of the inventor, expressed or inferred from the claims. This lies at the heart of Biovail's position that Novopharm's allegation that it will not infringe the '320 patent is not justified. Put another way, was it obvious at the time the patent was published that the substitution of a variant would make a difference?

8. To overclaim is to lose everything. If the inventor underclaims, the court will not broaden the monopoly in the interests of the "spirit" thereof. This often, as in this case, results in layers of claims, each limitation serving as a potential safety net so that if the broadest claims fall, the monopoly may be saved in part by the more modest claims.

9. Yet a patent is not an ordinary writing. It meets the definition of a "regulation" in the Interpretation Act, and must be read to assure the attainment of its objects. "Claims construction is a matter of law for the judge, and he was quite entitled to adopt a construction of the claims that differed from that put forward by the parties." (*Whirlpool*, para. 61.)

Patent Construction in This Case

[35] The relevant claims in the 546 Patent, claims 1, 2, and 6 read as follows:

Claim 1:

[R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-((1-methylethyl)-3-phenyl-4-[(phenylamino)-carbonyl]-1H-pyrrole-1-heptanoic acid or (2R-trans)-5-(4-fluorophenyl)-2-(1-methylethyl-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide; and pharmaceutically acceptable salts thereof.

Claim 2:

A compound of Claim 1 which is [R-(R*R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-((1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid.

Claim 6:

The hemicalcium salt of the compound of Claim 2.

Fortunately, these complex formulae have been given simpler names such that Claims 1, 2, and 6 can be read more easily as follows:

> Claim 1: Atorvastatin acid or atorvastatin lactone; and pharmaceutically acceptable salts thereof.
>
> Claim 2: Atorvastatin acid.
>
> Claim 6: The hemicalcium salt of the compound of Claim 2.

[36] The only claim in issue in these proceedings is Claim 6. It claims the hemicalcium salt of atorvastatin.

[37] Dr. Roush for Pfizer made the following remarks regarding a person skilled in the art:

> 57. I understand that the person of ordinary skill in the art is one who would share the expected common knowledge of competent ordinary workers within the field of the 546 Patent as of July 21, 1989. The "art" in this case is that of medicinal chemist, an important branch of organic chemistry that deals with the development of new drugs, typically by generating SAR data sets based on hard work and long hours in the laboratory.
>
> 58. The person of ordinary skill in the art would have at least a Bachelor of Science degree in organic chemistry, medicinal chemistry or related chemistry, coupled with several years of recent experience in synthesizing organic molecules.
>
> (A.R. Vol. 3 at 441.)

[38] Dr. Heathcock for Novopharm stated with respect to a person skilled in the art:

> 22. It is my opinion that one of the people to whom the '546 patent is directed is an organic chemist who is involved in the development and synthesis of complex organic molecules, including pharmaceutical active ingredients.
>
> 23. This person would have at least a Bachelor of Science degree, and more likely a post-graduate degree, in organic chemistry or medicinal chemistry along with several years of experience in synthesizing organic compounds.
>
> (A.R. Vol. 14 at 4661.)

[39] In other words, both parties generally agree that a person skilled in the art would be an organic or medicinal chemist – a person with at least a Bachelor of Science degree and with experience conceiving, creating, synthesizing and testing compounds to be used as medicines.

[40] Expert witnesses called as persons skilled in the art who attempted to interpret the patent were Dr. Roush, Dr. Spargo and Dr. Heathcock.

[41] Dr. Roush for Pfizer states the following:

> 63. The 546 Patent specifically discloses and claims atorvastatin calcium. The 546 Patent specifically discloses that atorvastatin has unexpected and surprising activity to inhibit cholesterol biosynthesis. In particular, the 546 Patent specifically discloses that atorvastatin has ten times the inhibitory activity (of the biosynthesis of cholesterol) as compared to a racemic mixture of atorvastatin and its corresponding S-trans enantiomer.
>
> 64. This increase in activity of atorvastatin over the racemic mixture is unexpected and surprising. A person of ordinary skill in the art would expect, at most, a two-fold increase in activity upon separation of the enantiomers from the racemic mixture. This two-fold activity increase assumes, however, that all of the activity of the racemic mixture resides in one of the enantiomers, the other one being totally inactive. In the case of atorvastatin, the S-trans enantiomer is not inactive. The data on page 8 of the 546 Patent shows that the S-trans enantiomer has activity. As such, the actual expected activity increase that a person of ordinary skill would anticipate for the more active enantiomer over the racemic mixture containing it would be less than two-fold. In this context, the ten-fold increase in activity is surprising and more certainly unexpected.
>
> 65. The 546 Patent identifies atorvastatin calcium as the most preferred embodiment of the invention at page 4 lines 21 to 24 wherein it states: "The most preferred embodiment of the present invention is [R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)-carbonyl]-1H-pyrrole-1-heptanoic acid, hemicalcium salt".
>
> (A.R. Vol. 3 at 442.)

[42] Dr. Heathcock for Novopharm essentially concurs:

> 94. The '546 patent suggests that the 3R,5R isomer (also referred to as the 3-(R)-trans isomer when in the lactone form) is 10-fold more effective in inhibiting HMGR than atorvastatin racemate. It further states that this "surprising inhibition" is "unexpected," and states that "an ordinarily skilled artisan may not predict the unexpected and surprising inhibition of cholesterol biosynthesis of the present

invention." In support of these assertions, the '546 patent provides on page 8 the following table of biological data:

Compound	IC_{50}, μM/liter
[R-(R*R*)] isomer (3R,5R)	0.0044
[S-(R*R*)] isomer (3R,5R)	0.44
Racemate	0.045

95. As expected, the assay shows that the 3R,5R enantiomer is the active enantiomer. On the basis of this data, the bioactivity of the 3R,5R enantiomer would appear to be 10-fold greater than that of the racemate. A person of ordinary skill in the art would typically only expect an improvement of up to 2-fold when comparing the active enantiomer to the corresponding racemate (that is, if all of the biological activity resides in the 3R,5R enantiomer and none in the 3R,5R).

(A.R. Vol. 14 at 4284.)

[43] In addition Dr. Spargo on behalf of Pfizer asserts:

30. The 546 Patent states (on page 3) that the invention provides for compounds consisting of atorvastatin, its lactone form, and pharmaceutically acceptable salts of atorvastatin. It is stated at page 4 of the 546 Patent that "the most preferred embodiment of the present invention is [atorvastatin] hemicalcium salt."

31. This would teach a person skilled in the art reading the 546 Patent that the hemicalcium salt of atorvastatin is preferred over all other salts. The 546 Patent therefore teaches persons skilled in the art to preferably use atorvastatin calcium.

32. The 546 Patent states that the atorvastatin enantiomer has approximately ten times the inhibitory activity of a racemic mixture. Any salts of atorvastatin would be expected to have the higher inhibitory activity than salts of the racemic mixture. Thus, when the patent states that the calcium salt is preferred, a person skilled in the art would understand that the preference necessarily refers to that salt's superior physical properties over the other salts of atorvastatin.

(A.R. Vol. 8 at 2393.)

[44] Upon reading the patent, and taking into account the expert advice so as to read it through the eyes of a person skilled in the art, the Court reads the disclosure as explaining the following:

- atorvastatin in its lactone form, its corresponding ring-opened acid form, and the pharmaceutically acceptable salts thereof is useful for lowering cholesterol levels in mammals, including humans.

- atorvastatin in its lactone form, its corresponding ring-opened acid form, and its pharmaceutically acceptable salts thereof provides an unexpected and surprising inhibition of cholesterol biosynthesis; unexpected in that it is ten-fold increase over the inhibition provided by the racemic mixture. The data for this ten-fold increase comes from a CSI screen disclosed in the 893 Patent. All compounds for the CSI screen were prepared as described in the 893 Patent.

- the most preferred embodiment of the invention described in the 546 Patent is the hemicalcium salt of the atorvastatin acid.

- the compounds of the lactone form, the corresponding ring-opened acid form, and the pharmaceutically acceptable salts thereof all have generally equivalent utility.

Selection Patent

[45] Pfizer claims that the 546 Patent is a selection patent. Specifically, Pfizer asserts in its factum:

> 2. The claim at issue in this proceeding is a claim to a selection invention. The claim to atorvastatin calcium (also called the hemicalcium salt of atorvastatin) is a selection of a compound having advantageous improvements from a broad class of thousands of compounds and salts described in a prior Pfizer patent (Canadian Patent 1,268,768 (the "768 Patent")). The invention is the selection of one specific compound, atorvastatin calcium, from that broad class of compounds and the recognition of its preferred physical properties and unexpected and surprising activity of atorvastatin calcium.
>
> 21. A person of ordinary skill would read and understand the 546 Patent as disclosing atorvastatin calcium as the particular salt form that exhibits the unexpected and surprising inhibition of cholesterol biosynthesis and having the most preferred physical properties. In terms of formulation, "most preferred properties" would be understood by persons of ordinary skill to represent the salt form with the best combination of physical properties -- including solubility, hygroscopicity, stability and processability.
>
> 37. … Thus, atorvastatin calcium not only has surprising and unexpected biological activity, it also has the best set of physical properties, <u>which was also surprising and unexpected.</u> In fact, it was the selection of the calcium salt which made atorvastatin a commercially feasible product for the first time.
>
> (A.R. Vol. 29 at 9940, 9945, 9950 [underlining added].)

[46] According to Pfizer, the 546 Patent reveals two special advantages of the hemicalcium salt of the atorvastatin acid over the rest of the group (in this case the racemic mixture of the atorvastatin and the S-trans enantiomer of the atorvastatin), namely:

> a. an unexpected ten-fold increase in activity when a person skilled in the art would have only expected a two-fold one, and
> b. the best combination of physical properties of this salt -- including solubility, hygroscopicity, stability and processability, over all the other salts mentioned in the 893 Patent.

[47] Novopharm disputes both of these claims. It alleges that the data regarding the ten-fold advantage is unreliable (more about that later) and that no special advantage regarding the hemicalcium salt of atorvastatin is provided within the 546 Patent.

[48] The rules for selection patents are well known and have their origin in *I.G. Farbenindustrie A.G.'s Patents* (1930), 47 R.P.C. 289 at 322 (High. Ct. Ch.) where Maugham J. observed:

> Three general propositions may, however, I think, be asserted as true: - First, a selection patent to be valid must be based on some substantial advantage to be secured by the use of the selected members. (The phrase will be understood to include the case of a substantial disadvantage to be thereby avoided.) Secondly, the whole of the selected members must possess the advantage question. Thirdly, the selection must be in respect of a quality of a special character which can fairly be said to be peculiar to the selected group.

[49] The rationale for such policy can be found in Lord Glaisdale's observation in *E.I. du Pont de Nemours & Co. (Witsiepe's) Application*, [1982] F.S.R. 303 at 313 (H.L.) [underlining added]:

> The type of invention which the law of selection patents was designed to foster appears from the speech of my noble and learned friend, Lord Diplock, in *Beecham Group Ltd*. v. *Bristol Laboratories International S.A.* [1978] R.P.C. 521, 579:
>
> > "The inventive step in a selection patent lies in the discovery that one or more members of a previously known class of products possess some special advantage for a particular purpose, which could not be predicted before the discovery was made (In re *I.G. Farbenindustrie A.G.'s Patents* (1930) 47 R.P.C. 283 per Maugham J. at pp. 322/3.) The *quid prop quo* for the monopoly granted to the inventor is the public disclosure by him in his specification of the special advantages that the selected members of the class possess."

[50] I propose to deal with these propositions in the reverse order. In light of the above jurisprudence, I have some trouble agreeing with the second proposition that the 546 Patent selects the hemicalcium salt of the atorvastatin acid from all the other pharmaceutically acceptable salts. Admittedly, the disclosure of the 546 Patent states at page 4, lines 21-24:

> The most preferred embodiment of the present invention is [R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)-carbonyl]-1H-pyrrole-1-heptanoic acid, hemicalcium salt.

[51] Dr. Spargo points out that a person skilled in the art would know that this refers to "that salt's superior physical properties over the other salts of atorvastatin" (A.R. Vol. 8 at 2394).

[52] Even Dr. Adelstein, Novopharm's witness conceded this point under cross examination.

> Q. This is teaching you that, of all the aspects of the invention that are disclosed in the '546 patent, the most preferred embodiment is the atorvastatin hemicalcium salt. Right?
>
> A. Yes.
>
> Q. You would agree then that, reading the '546 patent, the person of ordinary skill in the art would know that atorvastatin calcium is the most preferred embodiment of this invention?
>
> A. Yes.
>
> (A.R. Vol. 16 at 5066.)

[53] From the various experts, it seems clear that typically, the preferred properties of a salt are low hydroscopicity, good dissolution and good compaction. However, the 546 Patent does not tell the world in what way the properties of the hemicalcium salt are unexpectedly superior over other pharmaceutically acceptable salts. In other words, the patent does not disclose the special advantage peculiar to the hemicalcium salt that was hitherto unknown and that is revealed in the 546 Patent.

[54] I have no reason to reject Dr. Spargo's and Dr. Adelstein's explanation (that a person skilled in the art knows that 'preferred embodiment' refers to that salt's superior physical properties over the other salts of atorvastatin). However, this is not enough for a selection patent; it is an insufficient disclosure as the special characteristics of hemicalcium are neither identified nor quantified. The mere assertion that the hemicalcium salt of atorvastatin is the preferred embodiment of the invention does not meet the requirements of a selection patent. As Maughan J. specifically stipulated in *I. G. Farbenindustrie, supra* at 323 [underlining added]:

> I must add a word on the subject of the drafting of the specification of such a patent. It should be obvious, after what I have said as to the essence of the inventive step, <u>that it is necessary for the patentee to</u>

> define in clear terms the nature of the characteristic which he alleges to be possessed by the selection for which he claims a monopoly. He has in truth disclosed no invention whatever if he merely says that the selected group possesses advantages. Apart altogether from the question of what is called sufficiency, he must disclose an invention; he fails to do this in the case of a selection for special characteristics, if he does not adequately define them. The cautions repeatedly expressed in the House of Lords as regards ambiguity have, I think, special weight in relation to selection patents. (*Natural Colour etc. Ld. v. Bioschemes Ld.*, (1915) 39 R.P.C. 256, at p. 266; and see *British Ore etc. Ld. v. Minerals Separation Ld.*, (1910) 27 R.P.C. 33, at p. 47.)

[55] As the foregoing analysis has shown, the 546 Patent does not meet the requirements of a valid selection patent claim in terms of a salt selection.

Significance of Selection Patent

[56] The entire case stands or falls on the issue of selection patent and specifically the ten-fold increase in activity of one of the enantiomers over the racemate. If the 546 Patent is a valid selection patent, this is a complete answer to the allegations of anticipation, obviousness and double patenting. None of Novopharm's witness have asserted either:

a. that a ten-fold activity was anticipated on the basis of the 893 Patent;

b. that it was obvious to a person skilled in the art that resolving the racemate of atorvastatin would result in a ten-fold increase of activity by the enantiomer; quite the contrary they allege that a two-fold increase was to be expected; or

c. that the 441 Patent or the 768 Patent discloses or claims an enantiomer of atorvastatin that displays a ten-fold increase of activity of the enantiomer over the racemate.

[57] Pfizer in its first proposition asserts that the 546 Patent is a selection patent that selects atorvastatin in its lactone form, its corresponding ring-opened acid form, and the pharmaceutically acceptable salts thereof from the range of compounds described in the 893 Patent. According to Pfizer, the 546 Patent discloses an unexpected advantage hitherto unknown: the ten-fold increase in activity in lieu of the expected two-fold increase. Thus, the key issue becomes whether Novopharm can effectively challenge the 546 Patent as a selection patent; i.e., challenge the claim to the ten-fold increase in activity. In my view, it cannot for the following reasons.

I. Insufficiency of the NOA

[58] Novopharm in its NOA makes allegations of invalidity based on anticipation, obviousness and double patenting. The NOA makes absolutely no reference to selection patents or inutility. Nor is there any mention that the data used to support the selection patent is questionable, unreliable or unsupported.

[59] Novopharm takes the position that the NOA is not deficient. It argues that implicit in the allegations of anticipation, obviousness and double patenting is the allegation that the 546 Patent is not a selection patent. This selection patent is based on an alleged ten-fold advantage. That advantage depends on the CSI 118 data displayed in the disclosure of the patent. Therefore, although neither selection patent nor defective data are mentioned in the NOA, Novopharm maintains that they are implicitly 'in play' through the allegation of anticipation, obviousness and double patenting.

[60] Novopharm further asserts that it did not know that the issue of selection patents would be raised or that the support for the data was based on such fragile grounds until it received the affidavits from Pfizer and cross-examined on them.

[61] Finally, Novopharm argues that Pfizer was in no way confused, never complained about lack of specificity of the NOA and never brought a motion to that effect. Accordingly, Novopharm argues that it can lead evidence by trying to impugn the data of CSI 118.

[62] As a result, the main thrust of Novopharm's case consists of extensive evidence from experts regarding assays. They specifically criticize the CSI 118 assay that is the foundation of the ten-fold claim set out in the chart in the disclosure of the 546 Patent. Novopharm's contention is that the assay is very questionable, was never repeated and should not be relied on for a variety of reasons. However, that will be discussed more fully later on under the sub heading "CSI 118".

[63] The jurisprudence on NOAs is clear and firmly established. Strayer J.A. described the nature of NOAs in *Bayer AG v. Canada (Minister of National Health and Welfare)* (1995), 179 N.R. 122 at para. 13, 60 C.P.R. (3d) 129 (F.C.A.) [underlining added] as follows:

> In particular this Court in *Pharmacia Inc. et al. v. Bull (David) Laboratories (Canada) Inc.* (1994), 175 N.R. 334 (F.C.A), at p. 335, stated the following:
>
> > "It seems to us that while a notice of allegation does play an important role in the ultimate outcome of litigation of this nature, [it] is not a document by which the judicial review application may be launched under section 6 of the *Regulations*. That document was put in as a piece of evidence by the appellants; it originated with the application filed before the Minister. Because it is not a document that was filed with the Court but with the Minister, in our view the notice of allegation is beyond the reach of the Court's jurisdiction in a judicial review proceeding. That being so, the Court, in our opinion, lacks jurisdiction to strike out the notice of allegation."
>
> This clearly means that the Court has no jurisdiction to make orders concerning the filing of notices of allegation or requiring them to be perfected in some way. The principle is that, by the scheme of the *Regulations*, the notice of allegation precedes the institution of prohibition proceedings in this Court. <u>It forms part of the</u>

> background to that proceeding, perhaps what one might loosely refer to as part of the "cause of action". A court cannot order that a cause of action be created, or that it be created at a certain time, or in a certain way. It can only deal with it after it is created or allegedly created. Those who fail to file notices of allegation, or adequate notices of allegation, must assume their own risks when it comes to attacks on the adequacy of such allegations once prohibition proceedings are commenced before the Court.

[64] Rothstein J.A. (as he then was) added in *Procter & Gamble v. Canada (Minister of Health)*, 2002 FCA 290 (CanLII), [2003] 1 F.C. 402 at para. 22, 216 D.L.R. (4th) 376 (F.C.A.) [underlining added]:

> 22 However, the notices of allegation and the detailed statement of legal and factual basis for the allegation must provide all the facts the generic producer intends to rely upon in subsequent prohibition proceedings. It cannot rely on facts that exceed those laid out in its detailed statement. See *Merck Frosst Canada Inc. v. Canada (Minister of Health)*, *supra*, at para. 9 *per* Stone J.A.

[65] In support of its assertion that there was no surprise, Novopharm quotes Sharlow J.A. in *Pharmascience v. Sanofi-Aventis Canada Inc*, 2006 FCA 229 (CanLII), 352 N.R. 99 at paras. 23-24 [underlining added]:

> 23 … There are two senses in which a notice of allegation may be said to be "inadequate" or "insufficient". In these reasons, I am using those words as they are used in *AstraZeneca AB v. Apotex Inc.*, 2005 FCA 183 (CanLII), 2005 FCA 183 (and a long line of prior cases) to describe a judicial determination as to whether the person to whom the notice of allegation has sufficient information to determine whether to seek a prohibition order.
>
> 24 The same words are sometimes used in what I call their "secondary sense", to describe a situation where a non-infringement allegation is not justified because it fails to address a relevant patent claim, or because it is not capable of establishing non-infringement (for example, where it is based on an incorrect construction of a patent claim). A notice of allegation cannot be found to be inadequate or insufficient in that secondary sense without addressing the allegation on the merits.

[66] I don't think this case supports Novopharm's contention. While it is well established that a generic does not need to anticipate every possible defense a brand name manufacturer may raise (*Pfizer Canada Inc. v. Novopharm Ltd.*, 2005 FCA 270 (CanLII), 341 N.R. 330 at para. 16, 42 C.P.R. (4th) 97) it must however mention in its NOA the legal and factual basis of its allegation.

The contention about the allegedly flawed data supporting the ten-fold increase in activity claimed in the 546 Patent is part of what Strayer J.A. described as "part of the cause of action". Novopharm must allege in the NOA that this data is flawed or else the Court cannot deal with it.

[67] It is no defense to say 'we did not know how questionable the data is until we saw Pfizer's affidavits and cross-examined them'. Novopharm intends to market the bioequivalent of atorvastatin. The patent on its face is a selection patent of the 893 Patent and can only stand if it meets the selection patent criteria referred to above. Special advantage is obviously a key criterion and depends on the ten-fold increase in activity. It thus begs belief to suggest Novopharm did not know that the data evidencing the ten-fold advantage would be an issue.

[68] When asked during the hearing about this point; i.e. why Novopharm did not put the issue of selection patents and the data supporting the selection in the NOA, counsel for Novopharm gave the following revealing answer:

> THE COURT: ... You've heard Mr. Shaughnessy say absolutely outright to me, I asked: Isn't the '546 a selection patent? He said yes. That was your position. Mr. Shaughnessy; did I mishear you?
>
> MR. SHAUGHNESSY: That's right, my lord. I think we've taken a position, both Mr. Wilcox and I, and Ms. Block have said that on its face the patent is a selection patent.
>
> THE COURT: Right. So you're basically saying, no, it's not.
>
> MR. STAINSBY: We're not saying, no, it's not, I'm saying it wasn't apparent on the face of the patent at the time they served the NOA. [Notice of Application]
>
> THE COURT: And therefore you could not have put it in your NOA?
>
> MR. STAINSBY: Well, I suppose we could have. We could also have put in there that it failed for lack of sound prediction, it failed for insufficient disclosure. We could have put lots of things in there but we didn't because those were not claims that it was clear that we were going to have to make. . . .
>
> (Rough Draft, Day 3, Transcript at 64.)

[69] Yet later on in a further exchange Mr. Stainsby states:

> There has not been a hint of prejudice. All there is is a technical argument, which I say is wrong at law, to the effect that Novopharm because it didn't say in its NOA the '546 is an invalid selection patent cannot challenge the evidence that was put forward by Pfizer.

> Now, the main challenge to that evidence comes only after we see the evidence, because the patent on its face contains data which purports to show a ten-fold increase in activity of the R-trans over the racemate. …
>
> (Rough Draft, Day 3 Transcript at 66.)

[70] This in my view is not the right way of proceeding. Novopharm cannot first allege anticipation, obviousness and double patenting and then in response to evidence from Pfizer, attack the patent on what amounts to be an attack based on a lack of utility or sound prediction. The 546 Patent on its face is a selection patent. The expert witnesses from both sides had no difficulty in identifying it as such. If Novopharm is of the view that the selection is based on flawed data it has to allege it at the outset.

[71] I repeat what Strayer J.A. stated in *Bayer AG, supra*. [The NOA refers to]:

> "what one might loosely refer to as part of the 'cause of action'. A court cannot order that a cause of action be created, or that it be created at a certain time, or in a certain way. It can only deal with it after it is created or allegedly created."

[72] Since the data evidencing the ten-fold advantage was not challenged in the NOA, it does not form part of the 'cause of action'. The Court will take it as established. The Court will not take into consideration any part of the evidence or submissions that question the veracity, soundness or reliability of that data.

[73] For the reasons set out in paragraph 56 above, this position of the Court disposes of this case. However, in case the Court of Appeal is of another view, I will briefly review and deal with Novopharm's attack on the data underlying the ten-fold advantage.

II. Unsuccessful attack on CSI 118

[74] If the court were to accept Novopharm's argument regarding sufficiency of the NOA as set out in paragraph 59 above (which it explicitly does not do), an examination of the data underlying the ten-fold advantage is required. That advantage is based on the CSI 118 assay. Before delving into the CSI 118 assay, a few words on the background of assays might be in order.

Assays

[75] As part of the drug development process at any pharmaceutical company, compounds of interest are evaluated to determine whether they have any biological effect. Typically, these compounds are evaluated by means of assays.

[76] Assays, which are also referred to as "screens", are experiments conducted on test compounds to determine whether they have a particularly desirable characteristic. An assay will allow one to determine how effective a given compound is in inhibiting enzyme activity or an enzymatic process (cholesterol biosynthesis) by measuring its activity *in vitro* or *in vivo*. In *vitro*

screens are carried out in a test tube, culture dish or elsewhere outside a living organism. *In vivo* screens are carried out in a living organism.

[77] This invention involves enzymes, which are involved in converting compounds into other compounds. They act as biological catalysts that speed up the rate of a chemical reaction.

[78] HMG-Co-A reductase is an enzyme that catalyzes the conversion of HMG-CoA and NADPH into mevalonic acid (mevalonate). As such, one assay that can be used to assess activity of a potential HMG-CoA reductase inhibitor is to put it into a medium containing, among other things, HMG-Co-A, NADPH and HMG-CoA reductase, and then monitor the inhibitor's ability to stop or slow down the conversion of HMG-CoA into mevalonic acid (as compared to the same reaction conducted without the inhibitor). This type of assay is also referred to as the COR assay. The purpose of the COR assay is to measure the effect that a statin has on only one enzyme, the HMG-CoA reductase.

[79] Another type of assay is the Cholesterol Synthesis Inhibition (CSI) screen. It measures the effect of the test compound on the incorporation of radiolabelled acetate into nonsaponifiable lipids as a measure of the inhibitory activity of a test compound with respect to the entire cholesterol biosynthesis pathway. In other words, it measures the effect that a test compound, a "statin", has on the entire cholesterol biosynthesis pathway.

[80] For *in vitro* assays involving enzymes, the ability to inhibit the reaction of interest is typically expressed as the IC_{50} value. The IC_{50} represents the concentration of an inhibitor that is required for 50% inhibition of the enzyme in the *in vitro* assay. The control measures the amount of cholesterol (CSI assay) or mevalonic acid (COR assay) produced in the absence of a test compound. The lower the IC_{50} the more potent the compound, since less of the compound is required to cause 50% inhibition.

[81] Pfizer used these two *in vitro* assays, the COR assay and the CSI assay, to evaluate its "statins" and to test whether their potential HMG-CoA reductase inhibitors had activity. Once a test compound had shown sufficient inhibitory activity with respect to the cholesterol biosynthesis, it was tested using the COR screen.

[82] Initially, Pfizer relied on both the COR and the CSI assays to support the 546 Patent. However, as part of the litigation Pfizer re-examined the COR evidence. It found that:

a. The data was not properly graphed;

b. The IC_{50} values were calculated by taking the inverse log of the concentrations in error; and

c. In the case of COR 111, an error was made in preparing the stock solutions of the racemic calcium salt.

(See Dr Newton A.R. Vol. 29 at 9778-79; Dr. Dietschy A.R. Vol. 29 at 9781-82.)

[83] As a result of these concrete errors, Pfizer abandoned the COR assays and no longer relies on them to support the 546 Patent.

[84] Pfizer however, still relies on the CSI assay. Novopharm alleges that it should not be relied on as well.

[85] Novopharm's attack on the CSI 118 assay involves the following allegations:

a. 118 is a single assay, there is no evidence that it has been replicated, therefore, one should not rely on it;

b. The lab notes for CSI 118 are deficient and not scientifically kept;

c. The lab technicians were not called notwithstanding that they are available. One of the technicians is still in Pfizer's employ, while the other technician lives in Michigan;

d. No margin of error was established for the CSI 118 test, yet this is standard for scientific tests;

e. CSI 118 cannot be relied upon as the test compounds did not fully dissolve in the buffer solutions and the concentrations of the compounds in the solution were not measured;

[86] An examination of the affidavits and the cross-examinations of Pfizer's experts reveal that the assays were no models of scientific testing. However, the criticisms by Novopharm's experts are limited to the methodology used. They suggest that a different and more rigid methodology of assay testing should have been used which would have led to different outcomes.

[87] Surprisingly, Novopharm, who wants to sell the bioequivalence of LIPITOR offered no evidence of its own as to either solubility and/or increased activity. It produced no evidence obtained using its own efforts that could be compared to the CSI 118 assay. Thus, the only evidence available to the Court is the data furnished by Pfizer, the affidavits commenting on the data and the cross-examinations on those affidavits. There is no counter evidence of any kind.

[88] The most severe criticism of Novopharm's experts concerns the dissolution of the compound in the buffer solutions.

[89] Novopharm's experts contend:

a. Dr. Heathcock (A.R. Vol. 14 at 4297):

113. As noted above, in order to obtain accurate IC_{50} values, one needs to know the concentration of the test solutions. As acknowledged by Dr. Newton in his affidavit, Pfizer did not determine the concentrations of its test solutions. This is especially troubling

considering that Pfizer's lab notebooks for CSI 118 (Appendix J to the Newton Affidavit) indicate that some of the test compounds were insoluble in the solution used to make up the assays ("stock solution").

114. More specifically, the lab notebooks indicate that the stock solutions for atorvastatin calcium, the 3S,5S enantiomer and atorvastatin racemate calcium were all insoluble and that the stock solution for atorvastatin racemate sodium solution was only "partly soluble". It was not determined what amount of each test compound dissolved in each stock solution. The stock solution is used to make the assay solutions (i.e., aliquots of the stock solution are removed, put into a tube and further diluted to give the assay solution). In order to know the concentration of the assay solution, one needs to know how much compound was taken from the stock solution and put into the assay solution. If all of the compounds dissolve in the stock solution, it is easy to make an accurate determination. However, if not all of the compound has dissolved, one should measure the concentration of the assay solution in order to accurately determine its concentration. As Pfizer does not measure the concentrations of each assay solution, it is not clear what the concentration is for each assay solution.

116. Accordingly, without accurate information about the concentration of the solutions used in CSI 118, the IC_{50} values obtained in CSI 118 should be [sic] not be relied upon to support a 10-fold increase in activity of atorvastatin over the racemate.

b. Dr. Alberts stated (A.R. Vol. 15 at 4587):

55. In order for a compound to inhibit an enzyme, it must be in solution. It is not clear from Pfizer's lab books that all of the compounds tested by Pfizer had completely dissolved in the assay solution. If the compound has not all dissolved in the assay solution, this would impact the concentration of the compound which in turn would effect the IC_{50}. In other words, if the reported concentrations are incorrect, the IC_{50} would also be incorrect.

56. It is clear from Pfizer's lab books that the compounds did not all dissolve in the stock solution. For instance, CSI 118 describes the solutions as insoluble and requiring sonication. The stock solution is used to make the assay solutions (a small amount of the stock solution is removed and diluted to make the assay solutions). Therefore, if the compound has not all dissolved in the stock solution it would be difficult to know that one has transferred the correct amount of the compound to make the assay solutions. The concentration of the assay solutions is critical to obtaining accurate IC_{50} values. Based on my review of Pfizer's assay results, I question whether they had transferred the correct amount of compound into each assay solution.

71 (vi). It is also not clear that the assay solutions had the reported concentrations. I note that the stock solution for atorvastatin racemate calcium, atorvastatin calcium and the calcium salt of the S enantiomer are described as insoluble. There is no indication as to whether all of the compounds were dissolved in the assay solutions. Again, for such an important assay, I would have expected Pfizer to confirm that the concentrations of the assay solution were correct …

74. As well, it is my opinion that Dr. Dietschy should not assume that CSI 118 used uniform suspensions simply because the laboratory notebook contains no notation as to whether or not there were undissolved lumps in the stock suspension. I question the correctness and reliability of the notes given the errors apparent in Pfizer's assays and laboratory techniques employed. Further, the notes for CSI 118 do not say a "uniform suspension" was achieved. While a homogenous suspension may be acceptable to determine whether a compound has activity, it is my opinion that it should not be relied on for quantitative analysis (i.e., to discriminate between 2-fold and 10-fold activity). For a quantitative analysis, a solvent system should be used which completely dissolves the compound.

c. Dr. Weinstock (A.R. Vol. 16 at 5101):

101. … In order to inhibit an enzymatic reaction, the drug must get to the enzyme, and the only reliable way for that to occur is for the drug and enzyme to be in common solution and for all the drug to be dissolved in the solution.

103. … The protocol for drug dissolution did not specify that the drug was to be ground before use, or how long attempts to dissolve drug should continue. From this, I conclude that a large variation in the amount of drug dissolved could have occurred during preparation of drug "solutions" to be used in the bioassays. …

104. … You would therefore expect the IC_{50} values to be the same for both the sodium and calcium salts as they would both be potassium salts in the solution. This was, however, not observed and, therefore, I question the reliability of the assay results obtained by Pfizer.

108. Note that atorvastatin racemate calcium, atorvastatin calcium, and the S-enantiomer calcium are all insoluble in Step 1, and that atorvastatin racemate sodium is milky and only part soluble in Step 2. Assuming that all the drug dissolve, if all the activity of the racemic compound resides in atorvastatin, then the atorvastatin sodium would have an IC_{50} of 4.72 nM which is 5 times **more** potent than atorvastatin calcium. Since under the conditions of the experiment all the soluble

salts exists as the equilibrium mixture of all the different salts in the test solution (as explained above), atorvastatin will be equally active regardless of the salt form in which it was dosed. This suggests that in this experiment only 1/5 of atorvastatin was dissolved for atorvastatin calcium and able to inhibit the enzyme. Since this is the data on which the claim that atorvastatin is ten times more potent than the racemic form is based, this claim is not correct.

d. Dr. Ness (A.R. Vol. 17 at 4587):

41. It should be noted that the solubility of the various atorvastatin preparations (including the atorvastatin racemate preparations) appears to have been a significant problem with the Pfizer assays. Many of these test compounds are very lipophilic and non-water soluble. According to paragraph 58 of the Newton Affidavit, Pfizer appeared to be satisfied with preparations of dispersed suspensions (i.e. solutions in which the test compound was not fully dissolved). However, using non-homogeneous suspensions could result in variations in the concentration of compound in the assay solutions, leading to wide variations in the results obtained.

42. There is not sufficient information provided in Pfizer's lab notebooks for me to determine whether Pfizer's solutions were homogeneous or not. Further, if I was alleging that an enantiomer had a 10-fold increase in activity over the racemate, I would have ensured that a solvent was used that completely dissolved the compound. Without doing so, I would not consider the assay results to be reliable.

[90] Pfizer's expert counter these criticisms as follows:

a. Dr. Newton (A.R. Vol. 4 at 746):

58. When attempting to solubilize a test compound, the objective was to obtain a clear solution. If a clear solution was unattainable, the secondary objective was to prepare as finely a dispersed suspension of the compound as possible. Such a suspension was acceptable for use in the assays. A suspension would be unacceptable for use only if it contained "chunks" of test compound.

61. The concentration of the test compounds in the stock solution or serial dilutions was not determined prior to testing in the CSI or COR assays. To do so would have been expensive and cumbersome and was not a routine step in the drug discovery process at Warner-Lambert or at other pharmaceutical companies.

b. Dr. Newton (A.R. Vol. 7 at 1970):

17. We did not determine the concentration of each salt of every test compound as such a procedure would have been time consuming and

atypical of the drug discovery process at the time. Today there are automated techniques for taking such measurements, but in the mid-1980s such techniques were unavailable. In any case, it was not necessary to know the precise concentration of the test solution to find the IC_{50} values and to compare those IC_{50} values in a head-to-head assay run on the same day. The reason this was not necessary was because we were only interested in the relative IC_{50} values and not the absolute IC_{50} values.

29 (e). Dr. Alberts states at paragraph 71(vi) that he would have expected the Warner-Lambert scientists to confirm that the concentrations of the assay solutions were correct. As discussed above, given the nature of the drug discovery program and the importance of rapid throughput, we did not confirm the concentrations for every assay. That was not routinely or easily done at the time.

c. Dr. Dietschy (A.R. Vol. 17 at 2096-98):

58. In addition to opening the lactone ring (if necessary) prior to testing, the test compounds also had to be solubilized into either a solution or a suspension (because they would have been provided by the chemists in powdered form). Statins are not readily soluble in many common solvents, and although the techniques for solubilizing them were well known at that time, I would expect to see variation in the quantity of test compound actually solubilized depending on the solvents and techniques used.

59. Because statins are relatively insoluble molecules, solubility problems were very common. This does not mean that all test results involving statins are invalid, however. On the contrary, anyone who has worked with statins over the last 30 years has had to deal with problems of solubility, and it was (and is) routine to sue solubilizing agents (such as PEG, detergents or albumin) to assist in obtaining a uniform dispersion of the statins in a particular solvent.

60. In order to test a statin in one of these assays, one needs to get the compound into some sort of uniform state so that the amount of compound being introduced into each assay tube is known. This is essential for looking at comparative data and can be done in a number of ways.

61. Ideally, the compound can be completely dissolved to give a clear stock solution. Often, however, this does not happen spontaneously due to the limited solubility of statins. The technician preparing the stock solution may therefore try sonication or vortexing in order to achieve a uniform dispersion in an aqueous phase. These stock solutions will look slightly opalescent or milky but will show no manifestation of gross lumps. These stock solutions would be acceptable. The worse-case scenario would arise when all of the common solubilization techniques have been tried but gross lumps of material remain. Such a stock solution would be unacceptable.

62. I understand that the Warner-Lambert technicians who prepared the stock solutions did not measure the solution concentrations after solubilizing the candidate drug compounds. In my view, it is the usual practice not to do this. I do not know of anyone, either in the industry or in academics laboratories, who would routinely carry out such a procedure. In any case, it is not necessary that the concentration of the compounds in the stock solution be measured. If one has a solution or uniform suspension, each aliquot will very accurately deliver a uniform amount of the compound in a known volume, either to the *in vitro* or the *in vivo* assay systems. Once an aliquot of the statin is delivered to the assay system, it undergoes some degree of dilution, allowing the bulk of the statin to be dissolved.

63. Furthermore, it would be incredibly expensive and difficult to actually measure the concentration of the test compounds in each of the hundreds of assays run. Those techniques would have been very tedious and difficult from a practical standpoint of drug discovery, and would have slowed down the entire procedure by months.

d. Dr. Dietschy (A.R. Vol. 17 at 2242):

21. Dr. Alberts states at paragraphs 55-59 that the test compounds were not sufficiently soluble to permit the data to be relied upon, and further, that other solvents should have been used. I disagree. The data show that the test compounds were sufficiently soluble in the solvents that were used in the Warner-Lambert protocol to cause inhibition of the enzyme. In this regard, I note Dr. Weinstock's comment at paragraph 101 of his affidavit where he suggests that for a drug to cause enzyme inhibition, *all* the drug must be dissolved in the solution. This is an overstatement. Obviously, some drug must be dissolved in order for it to reach the enzyme and inhibit it, but it is not necessary that all the drug be dissolved. Since the solubility of the calcium salts of the R-(R*,R*) enantiomer, the S-(R*,R*) enantiomer and the racemic mixture are the same, the inhibitory activity of these compounds could be validly compared.

[91] Pfizer's counsel characterized Novopharm's attack on CSI 118 as 'poking holes'. This is quite an apt description. Novopharm allegations certainly raise questions about the scientific rigour of CSI 118. However, these questions do not go so far as to totally discredit the assay or to establish that it is wrong.

[92] As the example of dissolution of the compound in the buffer solution demonstrates, the evidence of the experts is contradictory. In the absence of any evidence of their own, Novopharm's experts can only suggest such things as:

- " using non-homogenous suspensions could result in variations in the concentrations of the compound in the assay solution leading to wide variations in the results obtained. (Dr. Ness, A.R. Vol. 17 at 5400.)

- "The improper scientific protocol used by Pfizer demonstrates a general degree of sloppiness in the Pfizer laboratory and therefore leads me to disbelieve the results provided by Pfizer. I am confident that I would not be alone in this opinion. (Dr Alberts, A.R. Vol. 15 at 4716.)

- "After reviewing Pfizer's reply evidence, it remains my opinion that Pfizer's assay results cannot be relied upon to quantitatively determine the activity of one compound over another. The most that Pfizer's assay results can be used for is to determine whether a compound has activity but not to determine whether one compound has a two- fold, three-fold or ten-fold increase in activity over another compound." (Dr. Heathcock, A.R. Vol. 14 at 4319.)

(Underlining added.)

[93] If one takes a step back and looks at the overall situation, the following picture emerges. Pfizer produced the compound, tested it in the laboratory, produced data, interpreted the data and made certain findings, i.e., a ten-fold increase in activity of the R-trans enantiomer. There is no evidence that Novopharm produced the compound, tested it, collected data, or interpreted it. It merely had its experts examine the data and the methodology used to obtain it. Novopharm's experts criticized Pfizer's methodology and made certain assumptions, conjectures, extrapolations and drew conclusions. The nub of these conclusions is that employing a more rigorous scientific data would have revealed at best a two-fold advantage.

[94] Being faced with laboratory tests, data from the tests, the experts' interpretation of the data, and the experts' defence of the methodology employed on the one hand and on the other hand, no test, no divergent data, and only criticisms of the methodology employed and conjecture as to the results that may be obtained under a different methodology, the Court is driven to the conclusion that, on a balance of probabilities, Pfizer's data (although not perfect) together with the interpretation of its experts disproves the allegations of Novopharm (which are not backed by any laboratory evidence whatsoever).

[95] Thus, in the alternative, even if the NOA was found to be sufficient, the 546 Patent is still a valid selection patent, as the allegations by Novpoharm questioning the data of the ten-fold advantage can not be sustained.

Conclusion re Anticipation and Obviousness

[96] As mentioned above, the 546 Patent is a selection patent claiming a ten-fold advantage of the atorvastatin calcium (the R-trans enantionmer) over the racemate of atorvastatin calcium. This is the surprising and unexpected advantage that the enantiomer has over the other members of its class. For the reasons given above (either failure to allege anything about the selection patents and unreliable data in the NOA or the lack of contrary evidence disproving Pfizer's claim of ten-fold increase in activity) there is no need to examine in further detail the allegations of anticipation or obviousness. Novopharm has not presented any evidence whatsoever that the ten-fold advantage was either:

1. anticipated in the 893 patent; or

2. obvious in light of the state of the art in July 1989.

Double Patenting

[97] A few words about the issue of double patenting are required. Novopharm alleges that the 546 Patent is void for double patenting. Particularly it argues that with respect to the 441 Patent:

> 161. The '441 Patent was filed February 7, 1989 and claims priority to February 1, 1989 (almost 6 months prior to the filing of the '546 Patent). It provides a purportedly novel process for making atorvastatin. The '441 Patent teaches a person of ordinary skill in the art:
>
> a. the preferred enantiomer is the 3*R*,5*R*-dihydroxy acid;
> b. the compounds may be in their lactone form, their 3*R*,5*R*-dihydroxy acid form, or as a base addition salt of the acid;
> c. the acid form may be made by stopping the reaction prior to forming the lactone;
> d. alternatively, the acid form may be made by conventional hydrolysis of the lactone;
> e. the 3*R*,5*R*-dihydroxy acid may react to form salts with pharmaceutically acceptable metal and amine cations;
> f. the formation of pharmaceutically acceptable salts is done using conventional means; and

g. the term "pharmaceutically acceptable metal salt" contemplates salts formed with the calcium, sodium, potassium, magnesium, aluminium, iron and zinc ions.

164. Because the processes disclosed in the '441 Patent inevitably make atorvastatin, it is irrelevant that the '441 Patent only has process claims. The '441 Patent contains specific claims to a process for making atorvastatin, and not to making other compounds. The determination of which form of atorvastatin to use required no inventive ingenuity but merely the application of method.

(R.R. at 54-55.)

[98] With respect to the 768 Patent, Novopharm argues:

165. In view of Pfizer's position that the '768 Patent claims atorvastatin racemate and atorvastatin and its pharmaceutically acceptable salts, the '546 Patent represents an improper evergreening on the claims of the '768 Patent.

166. For the same reasons that the '546 Patent is anticipated by the '893 Patent, it represents an impermissible, co-terminus double patenting over the '768 Patent.

167. For the same reasons that there is nothing inventive in the '546 Patent over the '893 Patent, the '546 Patent is invalid for obviousness-type double patenting over the '768 Patent.

(R.R. at 56.)

[99] There are two types of double patenting, same invention double patenting and obviousness double patenting. (See *Whirlpool, supra* at paras. 63 -70)

[100] In same invention double patenting, the claims must be identical or co-terminus. Since the 441 Patent is a process patent, it is obviously not the same as the 546 Patent, which claims a compound. Given that the 546 Patent is a selection from the group of compounds disclosed in the 768 Patent (the Canadian equivalent of the US 893 Patent), the 546 Patent is obviously not identical with the claims of the 768 Patent.

[101] As far as obviousness double patenting is concerned, the claims or disclosure must exhibit novelty or ingenuity in order for the second patent to be valid. (See *Sanofi-Synthelabo Canada Inc.*, *supra* at para. 86).

[102] As the Court found that the 546 Patent was a selection patent, by definition it is novel and unexpected. It thus cannot be invalid on the basis of obviousness double patenting.

Overall Conclusion

[103] For the reasons stated above, Novopharm's allegations have been disproved and the prohibition order sought will be granted.

ORDER

THIS COURT ORDERS that:

1. The Minister of Health may not issue an NOC to Novopharm in respect of the proposed tablets for oral administration comprised of atorvastatin calcium in 10 mg, 20 mg, 40 mg, and 80 mg strengths until after expiry of Canadian Patent No 2,021,546; and

2. Novopharm shall pay Pfizer its costs of this application.

"Konrad W. von Finckenstein"

Judge

Annex 1

2. The 546 Patent is Not Valid

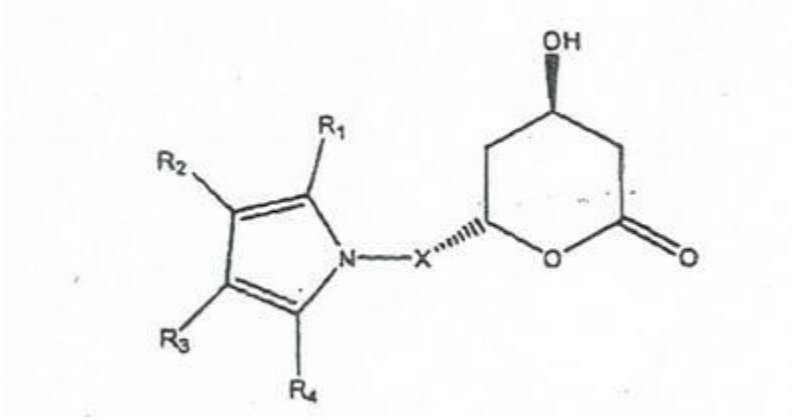
The claims of the 546 patent are not valid for the following reasons:

1. The claims are anticipated.
2. The claims are obvious.
3. The claims are double patented.

2.1 Anticipation

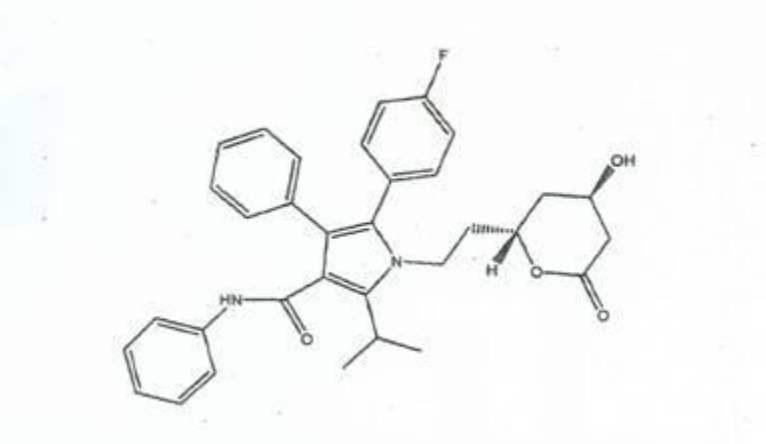
US Patent No. 4,681,893 (the "893 patent"), which issued on July 21, 1987, discloses certain trans-6-[2[(3- or 4-carboxamidosubstitutedpyrrol-1-yl)alkyl]-4-hydroxypyran-2-ones and the corresponding ring-opened acids. The 893 patent was listed by Pfizer on the US Orange Book for LIPITOR. The Canadian equivalent to the 893 patent is Canadian Patent No. 1,268,768 (the "768 patent") which is listed on the Canadian Patent Register for LIPITOR. By listing the 768 patent on the Canadian Patent Register and the 893 patent on the Orange Book, you have taken the position that both the 768 patent and the 893 patent claim Atorvastatin Calcium as distinct from mixtures of the RR trans and SS trans enantiomers.

Specifically, at column 2 of the 893 patent, it provides the following structure for the compounds claimed in the 893 patent:



As required by United States Law, the 893 patent also discloses methods for making these compounds and their corresponding ring-opened acid forms in sufficient detail to allow persons skilled in the art to make them as of the date the 893 patent became publicly available. To the extent that any steps are not explicitly described, these steps would have been well known to persons skilled in the art. As such, since you have taken the position that the 893 patent relates to Atorvastatin Calcium then it must be your position that a person skilled in the art would have been able to make Atorvastatin Calcium as well as the racemic mixture of Atorvastatin Calcium and its SS trans enantiomer as of that date.

Table 1 of the 893 patent discloses a number of examples which are representative of the compounds within the scope of the 893 patent. Compound 1 of Table 1 is described as having the following structure:



As noted above, the 893 patent discloses and claims the lactone ring forms (the ring-closed lactone form) of various compounds as well as their corresponding ring-opened acids (the ring-opened form). The 893 patent also discloses how to prepare both forms of these compounds.

The 893 patent also discloses that the ring-opened acids corresponding to the lactone forms of the compounds of the invention may be used as their pharmaceutically acceptable salts and more specifically as their metal or amine salt. The 893 patent discloses that the metal salt can be the sodium, potassium, calcium, magnesium, aluminum, iron, and zinc salt and that the amine salt may be formed with ammonia or organic nitrogenous bases strong enough to form salts with carboxylic acids. The 893 patent also discloses how to make the metal salts. For instance, Example 2 describes a process for making the sodium salt of 2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid.

The 893 patent also discloses that the compounds of the 893 patent:

1. are potent inhibitors of cholesterol biosynthesis by virtue of their ability to inhibit the enzyme 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA reductase);[1]

2. can be used as hypolipidemic or hypocholesterolemic agents in pharmaceutical compositions comprising a hypolipidemic or hypocholesterolemic effective amount of the compound in combination with a pharmaceutically acceptable carrier; and

3. can be used to inhibit cholesterol biosynthesis in a patient in need of such treatment by administering an effective amount of a pharmaceutical composition containing these compounds.

As stated above, since it is your position that the 893 patent claims and discloses Atorvastatin Calcium, claims 1, 2, 6, 11 and 12 of the 546 patent would be anticipated by the 893 patent. As well, to the extent that claims 3 to 5 and 7 to 10 are relevant and are asserted as being infringed, they too are invalid as anticipated by the 893 patent for the same reasons as set out above.

2.2 Obviousness

We also allege that each of claims 1, 2, 6, 11 and 12 of the 546 patent (and claims 3 to 5 and 7 to 10 if relevant and asserted as being infringed) are invalid on the basis of obviousness. Prior to the relevant date of the 546 patent:

1. Trans-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-pyrrole-3-carboxamide (the ring-closed lactone form of trans-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)-carbonyl]-1H-pyrrole-1-heptanoic acid and the racemate of the RR and SS forms) was known, having been prepared in example 1 of the 893 patent.

2. The ring-opened form was also known as it and the process for its manufacture were described in the 893 patent.

3. As stated above, based on your position that the 893 patent discloses RR-trans-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)-carbonyl]-1H-pyrrole-1-heptanoic acid) (i.e., Atorvastatin), Atorvastatin was known having being disclosed in the 893 patent.

4. The use of trans-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)-carbonyl]-1H-pyrrole-1-heptanoic acid and, in view of your position as described above, Atorvastatin, in the form of their pharmaceutically acceptable salts was known having been disclosed in the 893 patent. Specifically, the sodium, potassium, calcium, magnesium, aluminum, iron and zinc salt forms had been disclosed in the 893 patent. The choice of which form to use (i.e., as the ring-closed form or as a calcium salt or as a sodium salt) is based on routine determinations that were well known to a person skilled in the art.

5. The use of trans-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)-carbonyl]-1H-pyrrole-1-heptanoic acid or its pharmaceutically acceptable salts as a hypocholesterolemic agent had been disclosed in the 893 patent.

6. The use of trans-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)-carbonyl]-1H-pyrrole-1-heptanoic acid or its pharmaceutically acceptable salts in a pharmaceutical composition had been disclosed in the 893 patent.

7. The use of trans-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)-carbonyl]-1H-pyrrole-1-heptanoic acid or its pharmaceutically acceptable salts for inhibiting cholesterol synthesis in a human suffering from hypercholesterolemia had been disclosed in the 893 patent.

8. More specifically, in view of your position that the 893 patent discloses Atorvastatin Calcium, then the use of Atorvastatin Calcium as a hypocholesterolemic agent, in a

pharmaceutical composition and for inhibiting cholesterol synthesis in a human suffering from hypercholesterolemia, had been disclosed in the 893 patent.

9. It is well known to person skilled in the art how to manufacture trans-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)-carbonyl]-1H-pyrrole-1-heptanoic acid in the ring-opened form, the ring-closed lactone form and as its pharmaceutically acceptable salts an, as well, Atorvastatin and its pharmaceutically acceptable salts in view of your position that the 893 patent discloses Atorvastatin Calcium.

10. Lastly, the stereochemistry needed in the dihydroxyheptanoic acid side chain in order to achieve the biological effect in the class of compounds that includes Atorvastatin was well known to person skilled in the art. Specifically, it was known that the β-hydroxy in the lactone ring (sometimes referred to as the 4 hydroxy group or the 3 hydroxy group) needed to be in the R configuration. It was also known that the two hydroxyl groups in the lactone ring needed to be in the trans configuration. For instance, in US Patent No. 4,474,971, it states:

> "The process of this invention provides that 2H-pyran-2-one derivatives exclusively in the 4R,6S configuration of the naturally occurring compounds (i.e., compactin) with none of the undesired stereochemical or optical isomers being produced."

As well, in the US Patent No. 4,375,475, it states:

> "However, it has been found that the 4R enantiomers of the trans racemates corresponding to formula I specifically inhibit with high potency the activity of 3-hydroxy-3-methylglutaryl-coenzyme A reductase, which is known to be the enzyme involved in the rate limiting step in the process of cholesterol biosynthesis."

Also, it was well known that the other HMG-CoA inhibitors in the same class of compounds as Atorvastatin such as lovastatin, simvastatin, pravastatin and compactin, all of which were known prior to the filing of the priority application for the 546 patent, all had the β hydroxyl in the R configuration and the two hydroxy groups were in the trans configuration relative to one another.

As such, based on the above, a person skilled in the art would have been led directly and without any difficulty to the RR trans form of 2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)-carbonyl]-1H-pyrrole-1-heptanoic acid (Atorvastatin) and its salts including the calcium salt over the SS trans form and its salts. As such, claims 1, 2, 6, 11 and 12 are obvious in view of the prior art and the common general knowledge of a person skilled in the art (as represented by the art set out in Schedule A). Also, to the extent that they are relevant and alleged to be infringed, claims 3 to 5 and 7 to 10 for the reasons given above are also obvious in view of the prior art and the common general knowledge of a person skilled in the art.

2.3 Double Patenting

The claims of the 546 patent are invalid for double patenting on the basis of Canadian Patent No. 1,330,441 (the "441 patent"). The 441 patent claims a process for making Atorvastatin in the ring-closed form, the ring-opened form and as its pharmaceutically acceptable salts. For instance, claim 14 claims a process for making Atorvastatin in the ring-closed form. As such, both the claims and the disclosure of the 441 patent disclose Atorvastatin and its pharmaceutically acceptable salts including the calcium salt. The 546 patent is therefore invalid for obviousness double patenting.

The claims of the 546 patent are also invalid for double patenting on the basis of the 768 patent. The 768 patent was filed in Canada on May 7, 1987 and issued on May 8, 1990. In view of your position as discussed above, the 768 patent discloses and claims trans-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)-carbonyl]-1H-pyrrole-1-heptanoic acid and its pharmaceutically acceptable salts including the racemate (a mixture of the RR and SS trans forms) and each of the enantiomers (i.e., the RR trans and SS trans enantiomers). As such, since the 768 patent claims Atorvastatin and its pharmaceutically acceptable salts, the 546 patent is also invalid for coterminous double patenting.

As well, the claims of the 546 patent are invalid for obvious double patenting based on the 768 patent. A person skilled in the art would know that the RR trans form is the preferred form based on the art disclosed in Schedule A. As such, a person skilled in the art would have been led directly and without difficulty to the claims of the 546 patent with the results that the claims of the 546 patent claiming Atorvastatin, its various salt forms and its ring-closed lactone form are not patentably distinct from the claims of the 768 patent.

Annex 2

For Pfizer

Dr. Dr. Bruce D. Roth: He is the inventor of the patent relating to LIPITOR. He is currently employed by Pfizer as Vice-President of Chemistry, Pfizer Global Research and Development. He has been working for Pfizer since 1999 when Pfizer acquired the Warner-Lambert Company. Previous to his current employment with Pfizer, he had been working for Warmer-Lambert Company since 1982. He holds a Ph.D. in organic chemistry from Iowa State University. He is the co-author of 8 review articles and approximately 50 scientific papers. He has also given many lectures and presentations at various universities and conferences in the United States and Canada. He also has received many awards, one of which was the Warner-Lambert Chairman's Distinguished Scientific Achievement Award, which he shares with Dr. Roger Newton. In 1999, he was named Inventor of the Year by the New York Intellectual Property Law Association.

Dr. Roger S. Newton: His field of experience is within the area of lipid biochemistry. He holds a Ph.D. in the area of lipid metabolism from the University of California. During his post-doctoral fellowship, he worked with compactin. From 1981 to 1998 he was employed by Parke-Davis, the pharmaceutical research division of the Warner-Lambert Company, in the Atherosclerosis Pharmacology Department. His mandate was to establish and lead a drug discovery program aimed at finding a chemical composition capable of being commercialized as a cholesterol-reducing drug. Along with Dr. Bruce Roth, he was awarded the Warner-Lambert Chairman's Distinguished Scientific Achievement Award.

Dr. William R. Roush: He is a chemist with almost 30 years experience in organic chemistry and medicinal chemistry. He is presently the Executive Director of Medicinal Chemistry at the Scripps Research Institute. He is also the Associate Dean of the Kellogg Graduate School at Scripps. He holds a Ph.D. in Chemistry from Harvard University. From 1978 to 1987 he was an assistant professor of chemistry and researcher at Massachusetts Institute of Technology. Thereafter, he became a Distinguished Professor of Chemistry at Indiana University, where he initiated a research program on the design and synthesis of inhibitors of cysteine proteases. He has given numerous lectures at universities and pharmaceutical companies. He has also published over 225 scientific papers and related publications dealing with organic synthesis and medicinal chemistry. He is the Associate Editor of the Journal of the American Chemical Society.

Dr. Michael P. Doyle: He is a Professor and Chair of the Department of Chemistry and Biochemistry at the University of Maryland, College Park. He has been a professor of chemistry since 1968. He holds a Ph.D. in organic chemistry from Iowa State University. He was also a Distinguished Professor of Chemistry at Trinity University for 13 years. Then he joined the faculty of the University of Arizona at a Professor of Chemistry. He is also the author or co-author of 10 books, including *"Basic Organic Stereochemistry"* (published by Jon Wiley and Sons, New York, NY, 2001). He has published more than 250 scientific papers and has served on the editorial boards of a number of publications. Throughout his career, he has received many awards.

Dr. John M. Dietschy: He is a Medical Doctor and a Professor of Internal Medicine at the University of Texas, Southwestern Medical Center. He holds the H. Ben and "Isabel T. Decherd

Chair in Internal Medicine at the University of Texas. He has been involved in research relating to medicinal substances that inhibit the biosynthesis of cholesterol for more than 40 years, including research on statins. During this time, he has worked with atorvastatin, simvastatin, mevinolin and fluvastatin. He has published 230 scientific papers, most of which deal with the biosynthesis and/or metabolism of cholesterol. He has received a number of prestigious professional honours and awards for his work on the control of cholesterol metabolism and regulation in animals.

Dr. Peter Lionel Spargo: He obtained his BA with First Class Honours in Natural Science (Chemistry) from Cambridge University in 1983 and was awarded a Ph.D. in Synthetic Organic Chemistry, also from Cambridge University in 1986. He joined Pfizer Ltd. in 1988 as a Medicinal Chemist. Within two years he transferred to Pfizer's Process (now Chemical) Research and Development Department, where he progressed from Laboratory Team Leader to Section Head, then Manager, then Director, and Ultimately Head of Department. During his time at Pfizer, he identified, developed, and scaled up manufacturing processes for new drug candidates. He led Pharmaceutical Sciences teams, which worked on developing optimum formulations of compounds. Salt and solid form selection has been a key element of almost every project he has been involved with. In 2003, he joined Scientific Update LLP as a Scientific Director, where he has been expanding Scientific Update's consultancy services.

Dr. Peter Howard Jones: He is a Medical Doctor and Associate Professor of Medicine at Baylor College of Medicine in the section of Atherosclerosis and Lipid Research. He is the Medical Director of the Methodist Wellness Services Weight Management Center and Co-Director of the Lipid Metabolism and Atherosclerosis Clinic. He graduated with a Bachelor of Science in Chemistry in 1974 from Washington and Lee University. He received an MD from Baylor College of Medicine and graduated at the top of his class in 1974. His medical practice focuses on preventive cardiology and obesity treatment. He has extensive experience with the diagnosis and management of lipid disorders, as well as pharmacology with cholesterol lowering agents including HMG-CoA reductase inhibitors. He has particular experience in the treatment of hyperlipidemia and in the clinical use of statins, including LIPITOR. He has been a principal investigator or co-investigator in at least 30 clinical trials involving statins. He has also participated in numerous scientific committees and has published 80 scientific papers and over 20 abstracts, most of which deal with clinical trials involving statins.

Dr. Christopher Bokhart: He is the Vice President of CRA International, an international consulting firm dedicated to advising clients and counsel in the areas of business evaluations, licensing, and litigation support services. During his tenure at CRA, he consulted with clients and counsel on business valuation issues, licensing, technology, commercialization and transfer, and market assessment. Prior to becoming a Vice President with CRA, he was an Executive Consultant with Peterson & Co. Consulting and then he became a Managing Director with InteCap, and he was one of the founding Principals of IPC Groups, LLC, a predecessor to InteCap.

Sam Gourdji: He graduated from McGill University with a Bachelor of Science degree. He obtained his Masters in Business Administration with a specialization in marketing from McGill University in 1982. He is employed by Pfizer Canada Inc. as the Vice-President Strategic Planning & New Product Development. From 1994 to 2000, he worked at Parke-Davis, a Division of Warner-Lambert Company, LLC as Director of Marketing. In that capacity, he oversaw the marketing for

LIPITOR/atorvastatin calcium and provided Canadian input to the global development of LIPITOR. As the Director of Marketing, he was responsible for reviewing and approving information concerning the marketing and commercial success of LIPITOR in Canada. During this time, he was also a member of the Canadian Joint Operating Committee on LIPITOR. In 1994 he accepted a cross-development position in Government Affairs/External Affairs. His role in this position was to help secure government formulary listings for Parke-Davis medicines.

For Novopharm

Dr. Clayton H. Heathcock: He is a chemist with over 40 years experience in organic chemistry and medicinal chemistry. He is currently a Professor in the Graduate School at the University of California at Berkeley and a consultant with a number of pharmaceutical and biotechnology companies. He is also a Chief Scientist with the Berkeley branch of the California Institute for Quantitative Biomedical Research. He holds a Ph.D. in Organic Chemistry from the University of Colorado. He has synthesized a number of structural analogues of compactin and evaluated their biological activity. In 1985 he, along with Terry Rosen, completed their synthesis of compactin and published the results as a preliminary communication. They also synthesized other stereoisomers of compactin and the completed results were published in 1987. They were granted a patent for their discovery of a stereoselective method for the synthesis of various compounds in this series. He has since received a number of awards for his work in organic chemistry.

Dr. Alfred Alberts: He is an independent pharmaceutical and scientific consultant and advisor in the field of drug research and drug design. He has over 45 years of experience in biochemistry and drug discovery. Between 1975 and 1995, he held positions of increasing responsibilities at Merck Research Laboratories, including the position of Distinguished Senior Scientist and the Vice-President in Biochemistry and Director of Natural Product Discovery. For 15 years, he was the leader of Merck's atherosclerosis program which developed the HMG-CoA reductase inhibitors, which are a class of drugs used to lower blood cholesterol. He also discovered lovastatin (also known as mevinolin), and is the named inventor. He has received numerous awards for his research on HMG-CoA reductase inhibitors and on lovastatin, including the Inventor of the Year Award, Intellectual Property Owners, Inc.

Dr. Gilbert W. Adelstein: He is a medicinal chemist with more than 21 years of experience in the design and synthesis of new pharmaceutical active ingredients. He has a Bachelor of Science in Pharmacy from the University of Illinois as well as a Master of Science and a Ph.D. in Medicinal Chemistry from the University of Michigan. He began working for G.D. Searle& Co. from 1968 to 1990 as a laboratory scientist and eventually elevated to the position of Assistant Director of Regulatory Affairs. His work at G.D. Searle & Co. included synthesizing new chemical entities in the gastrointestinal, cardiovascular, and central nervous system disease research areas and later on he was responsible for developing and implementing research plans. From 1990 to 1995, he was the Director of Chemistry at Ohmeda, Inc., Pharmaceutical Products Division, where he oversaw the research and development of novel anesthetics and analgesics. From 1995 to 2003, he was the Associate Director, Regulatory Affairs at Sanofi Pharmaceuticals Inc., the Director of Regulatory Affairs and Quality Technical Services at Forest Laboratories and a Project Consultant at Reliant Pharmaceuticals. Since 2003, he has been an independent consultant to pharmaceutical companies and other organizations on pharmaceutical development and medicinal chemistry issues.

Dr. Joseph Weinstock: He is an independent consultant having 45 years of industrial experience in medicinal chemistry and the design and synthesis of drugs. He received his Bachelor of Science degree from Rutgers University in 1949 and his Ph.D. in Organic Chemistry from the University of Rochester in 1952. From 1954 to 1956, he was an instructor in the Chemistry Department at Northwestern University where he taught general and organic chemistry. From 1956 to 2002, he was employed at Smith Kline & French, which later became GlaxoSmithKline (collectively, "SmithKline"). He started as a Senior Medicinal Chemist and became the Director of Medicinal Chemistry when he retired. While working with SmithKline, he was responsible for and contributed to a number of major research projects, including the design and synthesis of three marketed drugs. Recently, he has been a consultant for Glaxo Medicinal Chemistry Group doing cancer research. He is the author or co-author of at least 143 publications, most of which relate to the synthesis and design of new pharmaceutical compounds. He is also the inventor of at least US 112 patents and numerous foreign patents.

Dr. Gene C. Ness: He has been a Professor in the Department of Biochemistry and Molecular Biology, College of Medicine, University of South Florida since 1986. He received his Bachelor of Science in Chemistry in 1966 from Bemidji State University and his Ph.D. in Biochemistry in 1971 from the University North Dakota. His current research centers on the molecular mechanisms by which physiological factors, including insulin, thyroid hormone and dietary cholesterol, regulate the expression of HMG-CoA reductase. He was a Senior Research Scientist, Clinical Chemistry Research and Development, Dade Division American Hospital Supply. He is the author or co-author of over 90 publications in referred journals, 4 invited reviews, and over 80 published abstracts, and took part in approximately 60 invited talks and seminars. He has received at least 8 awards for his research accomplishments, relating primarily to his work on the regulation of cholesterol biosynthesis.

Dr. Peter Loewen: He received a post-Baccalaureate Doctor of Pharmacy Degree in 1996 in the area of pharmacotherapeutics from the University of British Columbia ("UBC"). He received a Bachelor's Degree in Pharmacy from UBC in 1993. He has been a Clinical Pharmacist specializing in pharmacotherapeutic management of adult internal medicine patients in the Vancouver Coastal Health Authority for the past nine years and an Associate Professor of Pharmacology at the University of British Columbia. Since 2001, he has also been the Coordinator of Clinical Pharmacy Services at the UBC Hospital. He also served as Coordinator of the Vancouver Hospital & Health Sciences Centre Hospital Pharmacy Residency Program from 2001 to 2005. As part of his responsibilities, he is a member of the Drug & Therapeutics Committee. This committee evaluates which drugs are appropriate to have on the hospital's formulary. He has also held the position of Clinical Assistant Professor, Clinical Associate Professor, and Associate Professor at UBC's Faculty of Pharmaceutical Sciences since 1996. He has published numerous peer-reviewed articles and abstracts, and spoken as an invited presenter at many conferences, including presentations on statins and cholesterol.

Dr. Lea Prevel Katsanis: He is an Associate Professor in the Department of Marketing at the John Molson School of Business at Concordia University where he teaches Advertising, Marketing Policy, and Personal Selling at the undergraduate level and Pharmaceutical Marketing and Sales Management at the graduate level. He obtained his B.A. in Economics from Vassar College in 1976

and participated in an International Management Program at the London Business School in 1978. He obtained a Masters of Business Administration in 1979 from the Stern School of Business at New York University. He also holds a doctorate in Business Administration from the Marketing Department from George Washington University. From 1979 to 1981, he worked for Merck Sharp and Dohme as a Market Research Analyst and was subsequently promoted to the position of Senior Product Specialist, Cardiovasculars, and then to the position of Associate Product Manager, Ophthalmics. He has also worked at The Schering Plough Corporation between 1981 and 1984 as a Management Associate and then as a Product Manager. Thereafter, in 1985, he worked at Phone-Poulenc Pharmaceuticals where he was a Product Manager.

FEDERAL COURT

NAME OF COUNSEL AND SOLICITORS OF RECORD

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