Date: 20080104

Docket: T-16-06

Citation: 2008 FC 13

Ottawa, Ontario, January 4, 2008

PRESENT: The Honourable Mr. Justice Barnes

BETWEEN:

PFIZER CANADA INC. and
WARNER-LAMBERT COMPANY, LLC

Applicants

and

THE MINISTER OF HEALTH and
APOTEX INC.

Respondents

REASONS FOR JUDGMENT

Introduction

[1] These proceedings were commenced by Pfizer Canada Inc. and Warner-Lambert Company, LLC (collectively, Pfizer) against the Minister of Health and Apotex Inc. (Apotex) under the *Patent Medicines (Notice of Compliance) Regulations* SOR/93-133 as amended (NOC Regulations). Pfizer seeks an order prohibiting the Minister from issuing a Notice of Compliance (NOC) to the Respondent, Apotex, until the expiry of Canadian Patent No. 2,021,546 ('546 Patent). Pfizer asserts that the '546 Patent is a valid selection patent which will be infringed if Apotex is permitted to produce the protected compound,

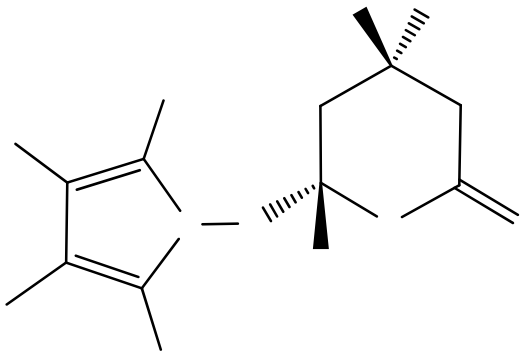
atorvastatin calcium (marketed as LIPITOR). Apotex, in turn, contends that the '546 Patent is invalid on several grounds including double patenting and the absence of a valid selection.

Background

[2] For the purposes of this decision, three related patents are at issue: U.S. Patent 4,681,893 ('893 Patent), Canadian Patent 1,268,768 ('768 Patent), and Canadian Patent No. 2,021,546 ('546 Patent). All of these patents were issued to Warner-Lambert Company. In 1999, Pfizer acquired Warner-Lambert and its subsidiaries, including Parke-Davis.

[3] The '893 Patent application was filed with the U.S. Patent Office on May 30, 1986 and issued on July 21, 1987. The corresponding Canadian application that led to the '768 Patent was filed in Canada on May 7, 1987, issued on May 8, 1990 and recently expired on May 8, 2007. I will refer to these patents collectively as '893 Patent.

[4] The '893 Patent is a genus patent that claims a class of compounds known as statins, which act to reduce cholesterol. The compounds described by the patent include those having the following structural formula:



[5] In the above structure, X is --CH2--, --CH2CH2--, --CH2CH2CH2-- or --CH2CH(CH3)-- and the R1, R2, R3 and R4 groups can be any one of a number of enumerated substituent groups.

[6] The class of compounds claimed by the '893 Patent includes the 4-hydroxypyran-2-ones, the corresponding ring-opened acids, and the pharmaceutically acceptable salts thereof. Practically, the compounds are most often used in their salt form. The pharmaceutically acceptable salts described in the patent include sodium, potassium, calcium, magnesium, aluminum, iron, and zinc ions.

[7] The '893 Patent also claims the individual enantiomers as well as racemic mixtures of the compounds described by the formula set out above. In particular, the patent covers the racemic mixture of atorvastatin.

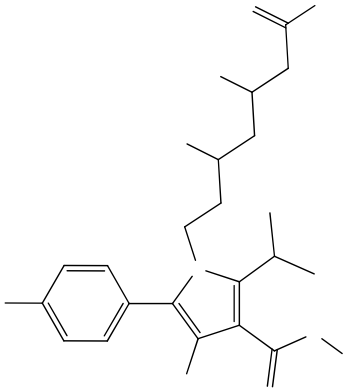
[8] Several years after the '893 and '768 Patent applications were filed, Pfizer filed a related patent application that issued as the '546 Patent. The '546 Patent claimed a narrow subclass of the compounds previously described in the '893 Patent based on a claimed unexpected advantage.

[9] One of the compounds taught by the claims of the '546 Patent is atorvastatin calcium, which is a salt. Atorvastatin is the medicinal ingredient in the anti-cholesterol drug LIPITOR.

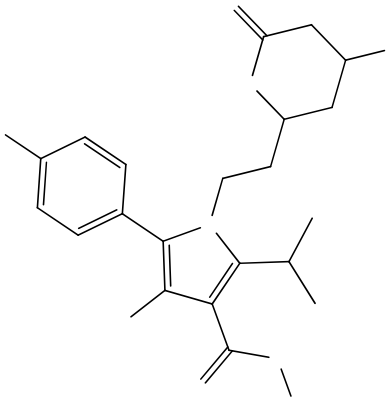
[10] The '546 Patent application was filed in Canada on July 19, 1990, based on a priority date of July 21, 1989. The patent was laid open to the public on January 22, 1991 and issued on April 29, 1997. It will expire on July 19, 2010.

[11] The '546 Patent claims one primary compound and several variations thereof. The basic compound is [R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-((1-methylethyl)-3-phenyl-4-[(phenylamino)-carbonyl]-1H-pyrrole-1-heptanoic acid. It exists in two primary

forms, covered by claims 2 and 3. Claim 2 protects this basic compound. This is often described as the acid form of atorvastatin, or more often, simply as atorvastatin:



[12] Claim 3 covers the lactone form, (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, known as atorvastatin lactone:



[13] The remaining claims identify particular salt forms of claim 2. The most important of these claims for the purposes of this proceeding is claim 6, the hemicalcium salt of atorvastatin (i.e. LIPITOR) which, according to Pfizer, is the best-selling drug in history.

[14] The “unexpected” finding of the '546 Patent was the “surprising inhibition of the biosynthesis of cholesterol” provided by atorvastatin beyond what would have been anticipated from the prior art including the '893 Patent.

Cholesterol-Inhibiting drugs

[15] Atorvastatin is a member of a class of pharmaceuticals known as statins, or HMG-CoA reductase inhibitors which are used to reduce cholesterol. Cholesterol is synthesized in most body tissues and is required for normal physiological functioning. It is carried through the bloodstream by two types of molecules: high density lipoproteins (HDL) and low density lipoproteins (LDL). LDL are known as the carriers of “bad” cholesterol because they can form a plaque on artery walls. This condition is known as atherosclerosis. If a clot forms, it is more likely to block off one of these narrowed arteries, and result in heart attack or stroke. It is thus desirable to reduce production of LDL.

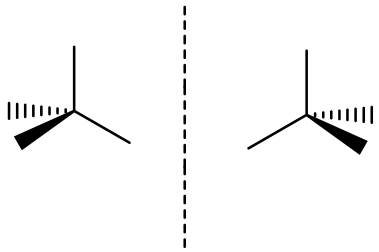
[16] A large amount of the body’s cholesterol is synthesized in liver tissue. The enzyme HMG-CoA reductase is referred to as the rate-limiting step, or the “bottleneck” in the cholesterol production pathway. HMG-CoA reductase catalyses the first reaction necessary in cholesterol synthesis, which is the production of mevalonic acid from HMG-CoA. This enzyme is the target of statins. Where statins are present, HMG-CoA reductase will bind preferentially with them over the HMG-CoA. This effectively slows cholesterol synthesis because there is not enough HMG-CoA reductase to perform the reactions. This is known as competitive inhibition.

Stereochemistry and naming of compounds

[17] A discussion of LIPITOR requires some background in stereochemistry, which is the study of the spatial arrangements of atoms within molecules. Molecules are described using chemical formulae that identify the individual atoms that make up the molecule. A given molecular formula may represent more than one possible arrangement of the atoms, in the sense that the atoms can be connected in different sequences with one another. Molecules with different absolute arrangements of atoms are called isomers. However, atoms may also be connected in the same order, but with differing three-dimensional arrangements. Two such molecules would be referred to as stereoisomers, which can be further classified as being disastereomers or enantiomers, depending on their characteristics. For the purposes of the '546 Patent, we are only interested in the latter.

[18] As molecules are three-dimensional in nature, and paper is only two-dimensional, chemists use certain conventions to depict the three-dimensional structure of molecules. As can be seen below, in general, a bond that is in the same plane as the paper is drawn as a

stick. To show a bond that reaches out of the page, a bold wedge is used. Where the bond goes below the plane (i.e., into the page), diminishing parallel dashes are used.

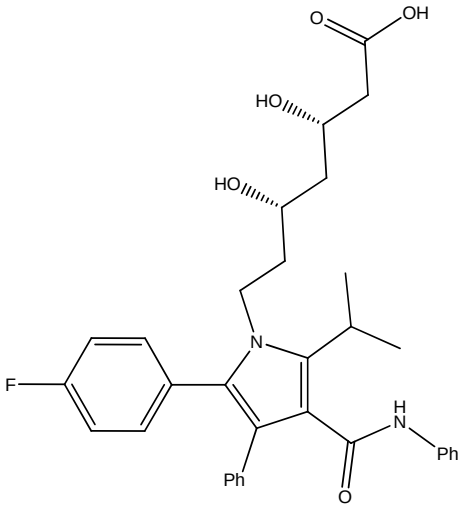


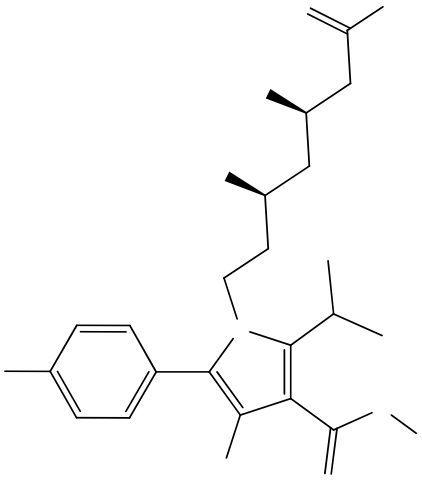
[19] The two molecules shown above are examples of enantiomers. The term "enantiomer" is used to describe the relationship between two stereoisomers which are mirror images of one another (that is, they cannot be superimposed on one another). A more obvious example of enantiomers is a pair of hands. The right and left hands are mirror images of one another and cannot be superimposed. Chemists refer to this non-superimposability as chirality.

[20] Enantiomers have identical chemical, spectral and physical properties but often possess different biological properties. For example, use of the drug thalidomide was curtailed when it was discovered that the supposed inactive enantiomer caused serious birth defects.

[21] A stereoisomer can exist in a racemic mixture (sometimes called a racemate), which is a mixture of equal parts of its two enantiomers. A racemate tends to have different physical properties from the individual enantiomers. Racemates can be separated or resolved to isolate the individual enantiomers.

[22] In the case of atorvastatin, there are not one but two chiral centres of interest, indicated by asterisks. The designation R(R*, R*) simply refers to the (R,R) enantiomer of a molecule with two stereogenic centres. The opposite of R(R*,R*) is S(R*,R*) which would actually indicate the (S,S) form. The following are respectively the R(R*,R*) and S(R*,R*) forms of atorvastatin in its acid form:





[23] For the purposes of this proceeding, in which only one set of enantiomers is of interest, the different structures are simply referred to as "atorvastatin" (indicating the R(R*,R*) enantiomer) and "the S-enantiomer of atorvastatin" (indicating the S(R*,R*) enantiomer).

[24] In this proceeding, Pfizer relies upon internal experimental data to support the promises of the '546 Patent. Apotex challenges the reliability of Pfizer's data and points to other research findings which, Apotex says, teach away from those promises. It is helpful, therefore, to understand the nature of the experiments conducted by Pfizer in connection with the claimed benefits of atorvastatin.

[25] In its drug development program, Pfizer used three different tests to assess the effectiveness of various drug candidates on cholesterol inhibition. The data referenced in the '546 Patent was derived from a Cholesterol Synthesis Inhibition (CSI) assay, but Coenzyme-A Reductase (COR) and Acute Inhibition of Cholesterol Synthesis (AICS) assays were also conducted.

[26] CSI and COR are both *in vitro* tests. In Pfizer's drug development program for LIPITOR, CSI was the first assay carried out. It was used to determine the effect of a drug candidate on the entire cholesterol synthesis pathway. In this assay, samples of the test compound, ideally at known concentrations, were added to a preparation of whole rat liver microsomes and cell enzymes. After the synthesis of cholesterol had proceeded for a given

period of time in two test tubes (one containing the test sample and the liver preparation, the other as a control, containing only the liver preparation) the amount of cholesterol in each tube was determined.

[27] The COR assays followed a similar process, but used a liver preparation which excluded enzymes other than HMG-CoA reductase. This way, the only step in cholesterol synthesis that could occur was the reaction of HMG-CoA into mevalonic acid, catalyzed by the HMG-CoA reductase. This reaction was allowed to proceed for a set period of time, after which the amount of mevalonic acid present was measured.

[28] In both the CSI and COR screens, the test value and the control value for each trial were compared to yield the percent inhibition of cholesterol (or mevalonic acid) synthesis. These values, for each of four different dilutions of test compound, were then graphed to find the concentration required for 50% inhibition of cholesterol - the IC_{50} value. This was the value of interest. A promising new medicine would hopefully generate a lower IC value indicating that a lower dosage would achieve the same reduction in cholesterol as other competing statins. A lower required dosage would typically improve the side-effect profile of the drug under consideration.

[29] Where positive results were obtained from the CSI and COR assays, a selected compound was then subjected to AICS screening. The AICS assay measured the amount of cholesterol produced by a rat *in vivo* after a single dose of the drug candidate. This would

indicate whether and to what extent the sample could be absorbed through the digestive system and delivered to the liver, where cholesterol synthesis occurs. In other words, the AICS screen established whether a compound was bioavailable. In this case, the relevant data – calculated in the same way as the IC_{50} values above – is the ED_{50}.

Expert Evidence

[30] With respect to the primary issue of the reliability of Pfizer's experimental data, it is important to keep in mind that the scientific witnesses were not speaking as "persons skilled in the art" but, rather were addressing basic issues of scientific methodology and interpretation. These are factual issues to be determined on a balance of probabilities. For ease of reference, the expert witnesses relied upon by each party in connection with the issues relevant to this decision are identified below with brief outlines of their respective qualifications.

Pfizer's Experts

[31] Dr. Bruce Roth: Dr. Roth is the listed inventor of the '546 Patent as well as 42 other patents. He has a Ph.D in organic chemistry and has been employed by Pfizer and Warner-Lambert since 1982, always working in areas related to blood cholesterol or atherosclerosis. Presently, he is the Vice-President of Chemistry, Pfizer Global Research and Development.

[32] Dr. Roger Newton: Dr. Newton obtained his doctorate in lipid biochemistry. From 1981 to 1998, he was an employee of Parke-Davis, the pharmaceutical research division of

Warner-Lambert. Dr. Newton held various positions at Parke-Davis. He was chairman of the atherosclerosis drug discovery team which developed atorvastatin calcium. He was also "product champion" of atorvastatin calcium and as such was responsible for convincing senior management to pursue United States FDA approval. He is now a senior vice-president of a Pfizer, Inc. company.

[33] Dr. John Dietschy: Dr. Dietschy is a medical doctor and a professor of internal medicine at the University of Texas. He has been involved in statin research for more than 30 years and has won numerous awards for his research on the control of cholesterol.

[34] Dr. William Roush: Dr. Roush is the Executive Director of Medicinal Chemistry at the Florida campus of the Scripps Research Institute. He has over 30 years of academic experience in organic chemistry and medicinal chemistry and has published extensively in these areas, and specifically in the area of synthesis and evaluation of optically active compounds. Dr. Roush also works as a consultant for various pharmaceutical companies, including Parke-Davis and its successors.

Apotex's Experts

[35] Dr. Paul Grieco: Dr. Grieco has 35 years of experience in synthetic organic chemistry and medicinal chemistry, with formal education in chemistry and organic chemistry. He was Chairman of the Department of Chemistry at Indiana University from 1988-1997. He is now a Regents' Professor in Montana.

[36] Dr. Robert Langer: Dr. Langer is an Institute Professor at the Massachusetts Institute of Technology (MIT). He has been recognized with a number of awards and in a number of popular magazines. He describes himself as an expert in areas including chemical engineering, biomedical engineering, biotechnology, pharmaceutical chemistry and formulation development. He has over 550 issued or pending patents worldwide. His formal education is in chemical engineering.

[37] Dr. John Keana: Dr. Keana is a Professor Emeritus at the University of Oregon, a consultant, and a member of the Editorial Board of *Medicinal Chemistry and Drug Design Review* online. He considers himself to be an expert in medicinal chemistry with a specialty in organic synthesis, stereochemistry, and lead optimization as related to drug discovery and development. He has a Ph.D in Chemistry.

Issues

[38] As in many applications of this kind, the parties have raised and argued numerous issues including the sufficiency of the Apotex Notice of Allegation (NOA), the legal significance of Pfizer's dealings with the Patent Office and the substantive validity issues of selection, double patenting, obviousness and anticipation. For the reasons which follow, it is only necessary to deal with the issues of sufficiency of the NOA and whether the '546 Patent is a valid selection patent. With respect to the issue of selection, the principal question for determination is whether Pfizer has established that atorvastatin calcium has surprising or

unexpected advantages sufficient to meet the legal requirements for a valid selection. This issue turns substantially on the adequacy and reliability of the experimental data marshalled by Pfizer to support the selection claims of the '546 Patent.

Analysis

Burden of Proof

[39] I am satisfied that Apotex has met its intermediate burden of proof and that Pfizer, in turn, has not satisfied the overall legal burden on a balance of probabilities that its '546 Patent is a valid selection patent.

The Expert Witnesses

[40] All of the scientific expert witnesses retained by the parties appear to be eminently qualified in their respective fields. I have identified nothing in the record to suggest that any of the witnesses was lacking in expertise or was unqualified to speak to the issues. My reasons for preferring the evidence of certain witnesses over that given by others are not, therefore, based on questions of qualification.

Sufficiency of NOA

[41] Pfizer argues that Apotex's NOA is insufficient to support an attack on the reliability of the research data cited in the '546 Patent in support of the promise of atorvastatin's unexpected and surprising cholesterol inhibiting properties. The basis of this insufficiency argument is that Apotex's "bald allegation" that the '546 Patent is not a valid selection has

no identified factual support. In the result, Pfizer says that the NOA could mean any number of things and Pfizer cannot be required to speculate on what was intended.

[42] In order to resolve this issue, it is necessary to consider Apotex's NOA selection allegations in tandem with the language of the '546 Patent and in the context of the conduct of the parties in this proceeding.

[43] The issue of selection is dealt with in the following passage from Apotex's NOA:

> Furthermore, the '546 Patent cannot be said to be a selection patent since the '546 Patent merely at best verifies the known properties of the previously disclosed compounds taught in the '893 Patent (and in the '768 Patent), that is the R form enantiomer of atorvastatin, and inhibition of cholesterol synthesis with the R form enantiomer of atorvastatin, and pharmaceutical compositions comprising the R form enantiomer of atorvastatin for the inhibition of cholesterol synthesis.
>
> There was no substantial advantage to be secured by the compounds claimed in the '546 Patent. The '546 Patent did not provide that the whole of the selected members possessed the purported substantiated advantage (if any).
>
> The selection (if any) was not made in respect of a quality of a special character peculiar to the selected group.
>
> All the advantages of the compounds claimed in the '546 Patent were known at the claim date of the '546 Patent and, if not, would have been obvious as evidenced by state of the art (common knowledge in the art) exemplified by the teachings of the references in Schedule A.
>
> We rely on our discussion of the '893 Patent (the U.S. equivalent to the '768 Patent) under the heading "Anticipation" for this allegation and in respect of the '768

> Patent as the teachings of the '768 Patent and the '893 Patent are equivalent.
>
> We also rely on our discussion of the state of the art, the common general knowledge of a person skilled in the art discussed under the obviousness section of this Notice of Allegation for this allegation.

[44] Apotex contends that the reliability of the research data is put in play by the allegation that there was no substantial advantage achieved by the invention and by its further reference to the "purported" substantiated advantage. Apotex also notes that the only evidence cited in the '546 Patent to support the promise of an unexpected advantage was the CSI data, so its allegation of "no substantial advantage" could only involve a challenge to that evidence.

[45] If I were convinced that Pfizer had been misled by the absence of an explicit challenge to the research data in the NOA, I would not hesitate to grant the relief it seeks. In these circumstances, however, I can find no evidence of prejudice to Pfizer and nothing to indicate that it misunderstood the nature of Apotex's selection challenge.

[46] I have no difficulty with the basic premise of Pfizer's argument that a NOA must contain both the legal and factual bases of each allegation. This requirement is, of course, directed at ensuring that a patentee has sufficient information to allow it to determine whether to seek a prohibition order: see *Pharmascience v. Sanofi-Aventis Canada Inc.*, 2006 FCA 229, 352 N.R. 99 at paras. 23-24.

[47] On the issue of the sufficiency of the NOA, Pfizer's Notice of Application asserted that "atorvastatin calcium has substantial and unexpected advantages which were neither known in the art nor obvious". In support of this allegation, Pfizer retained, among others, Dr. Dietschy to review Apotex's NOA. At para. 16 of his affidavit, Dr. Dietschy described his mandate as follows:

> I have been asked by counsel for Pfizer to comment on the data in the 546 Patent as well as other data referred to in this affidavit and to state my opinion whether, on the basis of that data, the inherent activity of atorvastatin - that is, its ability to inhibit cholesterol biosynthesis - is unexpected compared to the inherent activity of a racemic mixture of atorvastatin and the S-(R*,R*) enantiomer.

[48] Dr. Dietschy went on to opine that Pfizer's research data were adequate to support the promises of the '546 Patent. Apotex responded with its own evidence on this issue and the witnesses from each side were cross-examined. Not surprisingly, Pfizer has not produced any evidence that it was caught off-guard by the brevity of the Apotex allegations. Indeed, it was well aware that the adequacy of its research data had been a recurring theme in litigation involving this patent. Pfizer made an informed decision to address this issue in this proceeding and, having put the issue in play, it cannot later argue that Apotex is precluded from challenging the research data which ostensibly supported the selection promise of the Patent: see *Aventis Pharma Inc v. Apotex Inc.*, (2005), 43 C.P.R. (4th) 161 (F.C.) at para. 106 and *Novopharm Limited v. Pfizer*, (2005), 42 C.P.R. (4th) 97 (F.C.A.) at para. 17.

[49] In the result, I reject Pfizer's argument and find that Apotex's NOA is sufficient to support its challenge to the research data relied upon by Pfizer to support the claims of the '546 Patent.

The Law of Selection

[50] It is well understood that the selection of a chemical compound from a previously identified class of related compounds can be inventive and, therefore, patentable if the selection is both unobvious and advantageous. The criteria for creating a valid selection patent are described in the leading case of *Pfizer Canada Inc. v. Canada*, 2006 FCA 214, [2007] 2 F.C.R. 137:

> 3 There are two general classes of chemical patents. The first is the 'originating patent' where there is an originating invention involving the discovery of a new reaction or a new compound. The second is the 'selection patent', which is based on a selection from related compounds derived from the original compound and which have been described in general terms and claimed in the originating patent (see *In the Matter of I.G. Farbenindustrie A.G.'s Patents,* (1930) 47 R.P.C. 283 at page 321 per Maugham J.).
>
> 4 While there is little Canadian jurisprudence on the subject of selection patents, its elements are well defined in *I.G. Farbenindustrie*. Lord Diplock cited this decision with approval in the House of Lords where he stated that 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' (see *Beecham Group Ltd. v. Bristol Laboratories International S.A.* [1978] R.P.C. 521 at page 579). All claimed members of the known class must have the advantage and the advantage must not be one that those

skilled in the art would expect to find in a large number of the previously disclosed class (i.e. a quality of special character) (see *I.G. Farbenindustrie* at page 323).

5 Selection patents exist to encourage researchers to further use their inventive skills so as to discover new advantages for compounds within the known class. A selection patent can be claimed for a selection from a class of thousands or for a selection of one out of two (see for example *I.G. Farbenindustrie* at page 323 and *E.I. Dupont de Nemours & Co (Witsiepse's) Application*, [1982] F.S.R. 303 (H.L) at page 310).

…

21 It is important at the outset to establish that empirical research for the purpose of making a selection from a class is not verification. Lord Wilberforce in *Beecham* (supra at paragraph 4) noted that the selection of some from a larger number of possible components and the exploration of their appropriateness by empirical investigation is a different thing from verification and leads to different results (at page 568).

22 The empirical investigation leading to an invention protected by a selection patent must involve "at the least the discovery that the selected members possess qualities hitherto undiscovered, particular to themselves and not attributable to them by virtue of the fact of their belonging to a class specified by an earlier invention" (see *Dreyfus and Other Applications* (1945), 62 R.P.C. 125 at page 133 per Eversheed J.).

23 In *Pope Alliance Corporation and Spanish River Pulp and Paper Mills, Limited*, [1929] A.C. 269 (H.L.) Viscount Dunedin at pages 250-251 noted that "invention is merely finding out something which has not been found out by other people." An inventor is entitled to a patent where he can show that his efforts led to a discovery of certain knowledge central to his invention. It is no answer that others by experiment might have also found it (see also *T.A. Blanco White, Patents for Inventors and the Protection of Industrial Designs*, 5th edition: (London: Stevens & Sons, 1983) at page 99).

> 24 On the other hand, verification means confirming predicted or predictable qualities of known compounds; i.e. components that have already been discovered and made. No one can claim a selection patent merely for ascertaining the properties of a known substance (see *SmithKline Beecham Pharma Inc. v. Apotex Inc.* (2002), 21 C.P.R. (4th) 129 (FCA) at paragraph 21).
>
> …
>
> **31** To meet the statutory requirement in subsection 34(1) of the *Patent Act,* R.S.C. 1985, c. P-4 (old Act) that a patent be 'useful', the selected species must have an advantage over the class as a whole (see *Consolboard Inc. v. MacMillan Bloedel (Saskatchewan) Ltd.*, [1981] 1 S.C.R. 504 at pages 525-526). That case broadly defined the utility required for valid patent as discussed in *Halsbury's Laws of England* (3rd ed.), vol 29 at page 59:
>
> > ...it is sufficient utility to support a patent that the invention gives either a new article, or a better article or a cheaper article, or affords the public a useful choice.
>
> However, there are no special legal requirements regarding what particular type of advantage is required. The test for advantage is understood to include a disadvantage to be avoided, as is the case here (see *I.G. Farbenindustrie* at page 322).

[51] The often-cited case of *In the Matter of I.G. Farbenindustrie A.G.'s Patents,* (1930) 47 R.P.C. 283 refers to three general propositions that must be satisfied to create a valid selection patent. Firstly, the patent must disclose a substantial advantage to be secured by the selected members (or conversely the avoidance of a substantial disadvantage); secondly, all of the selected members must possess the claimed advantage; and, thirdly, the selection

must be in respect of a quality of a special character that is peculiar to the selected group. The Court concluded its selection discussion with the following admonition:

> 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, that it is necessary for the patentee to 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) 32 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)

The Application of Selection Principles to the '546 Patent

[52] It is common ground that atorvastatin calcium was a compound that fell within the broader class of compounds described by Pfizer's '893 Patent. Also falling within the scope of the '893 Patent were the S-enantiomer of atorvastatin calcium, the racemic mixture and several thousand other compounds. The '893 Patent claimed that all of the compounds of that invention "are useful as hypo-cholesterolemic or hypolipidemic agents by virtue of their ability to inhibit the biosynthesis of cholesterol". At the time, it would have been expected by persons skilled in the art that atorvastatin would have cholesterol lowering effects but at a level approximately double that of the racemic mixture.

[53] The '546 Patent acknowledged the promised utility of the compounds described by the '893 Patent in reducing cholesterol in humans but it went on to assert an unexpected finding that atorvastatin calcium "provides surprising inhibition of the biosynsthesis of cholesterol".

[54] The assertion in the '546 Patent that atorvastatin calcium exhibited unexpected and surprising inhibition of cholesterol biosynthesis was supported by experimental data set out in the following passage from the patent specification:

> The compounds according to the present invention and especially according to the compound of the formula I inhibit the biosynthesis of cholesterol as found in the CSI screen that is disclosed in U.S. Patent No. 4,681,893. The CSI data of the compound I, its enantiomer the compound II and the racemate of these two compounds are as follows:
>
> | Compound | IC_{50} (micromoles/liter) |
> |---|---|
> | [R-(R*R*)] isomer* | 0.0044 |
> | [S-(R*R*)] isomer | 0.44 |
> | Racemate | 0.045 |
>
> [*atorvastatin]

[55] These are critical representations for establishing the validity of the '546 Patent as a selection patent because, absent proof of a previously undisclosed and unpredictable special advantage (or a disadvantage avoided), Pfizer cannot re-patent atorvastatin calcium and Pfizer's monopoly over that compound would have expired with the expiry of the '893 Patent. This is a point conceded by Pfizer or, as it was put by its counsel, "this case stands or falls on the issue of selection".

[56] Before examining the accuracy of Pfizer's empirical assertions, it is necessary to construe the promise made by the '546 Patent.

[57] According to Dr. Dietschy, the '546 Patent promised only that atorvastatin calcium produces "much greater" or "disproportionate" inhibitory activity than a person skilled in the art would have expected. This is somewhat different than the evidence of Dr. Roush who seems to have read the research data cited as being part and parcel of the promise of the Patent. His affidavit stated that "the ten-fold increase in activity is surprising and most certainly unexpected". Pfizer argued that any material improvement over a two-fold increase in the inhibitory activity of atorvastatin calcium was essentially all that was promised. In that sense Pfizer now seeks to separate the inventive promise of the Patent from the data that were cited to support it.

[58] Although the '546 Patent did not expressly claim a ten-fold treatment advantage from atorvastatin calcium over the corresponding racemic compound, it is clear from the experimental data cited that a ten-fold *in vitro* advantage had been claimed. Although Dr. Roth was not speaking on behalf of a person skilled in the art, he described his initial findings as follows:

> 147. The data that I reviewed showed that there was almost a ten-fold difference in potency between the racemate and atorvastatin. These data were incorporated into a patent application for U.S. Patent 5,273,995 (995 Patent), which is the U.S. equivalent of the 546 Patent.

[59] It is implicit in the findings cited in the '546 Patent that the supposed unexpected efficacy of atorvastatin *in vitro* would result in substantially increased efficacy beyond the benefits already promised by the '893 Patent which included the expected two-fold advantage of atorvastatin over the racemic compound. The skilled reader of the '546 Patent would have no reason to question the validity of the data cited and would assume, in the absence of any qualifying statements, that Pfizer's research findings were accurate and reproducible. In other words, a person skilled in the art would conclude that Pfizer had actually found that atorvastatin was approximately 10 times more effective than the racemate in inhibiting the production of cholesterol *in vitro*. In the result, I do not accept Pfizer's attempt to decouple the promise of atorvastatin calcium's surprising and unexpected activity from the research data it cited in the Patent; but, in the end, it does not matter, if the evidence relied upon by Pfizer is so unreliable or untrustworthy that it fails to establish anything beyond a two-fold increase in the efficacy in atorvastatin over the racemate.

The Genesis of the '546 Patent Data

[60] The process by which the data used in the '546 Patent came to light was somewhat unusual. According to Dr. Roth, "someone" in attendance at Pfizer's Patent Review Committee, in response to a question by the Head of Preclinical Research, suggested that somewhere in the *in vitro* research data there may be evidence to show surprising biological activity for atorvastatin. Notwithstanding the fact that atorvastatin was Dr. Roth's compound, he was not aware of that data but he was asked to look for it. It is also clear

from Dr. Roth's evidence that Pfizer was, at that point, looking seriously at the possibility of preparing a patent application for atorvastatin and that Dr. Roth's search for supporting data was intended to determine if atorvastatin "possessed any surprising activities or properties that would make it patentable in and of itself".

[61] Dr. Roth testified that he knew that atorvastatin was already covered generically by the '893 Patent so when he went to investigate the research data he would have known that Pfizer could not re-patent that compound in the absence of evidence of some unexpected biological activity.

[62] Such an approach raises a concern that the investigator is analyzing and selecting data after-the-fact to prove inventiveness in support of a business decision instead of confirming the novelty of the research findings as the data is being obtained. Such a look-back approach requires rigorous objectivity and unimpeachable fidelity to scientific methodology by the investigator to exclude the possibility of tunnel vision.

The Reliability of the '546 Patent Data

[63] Dr. Roth's affidavit described the approach he took to selecting and analysing Pfizer's research data. He acknowledged that an "optimal comparison" would have required head-to-head assays of both enantiomers of atorvastatin and its racemate but, at the time, he could not find such a comparison. He therefore compared the head-to-head assays for the sodium salts of the two enantiomers (CSI 120) with the average of the historical data from

assays for the racemic sodium salt of atorvastatin (CSI Nos. 92, 93, 95, 102 and 118). The five assays of the racemic sodium salt were not run head-to-head and were conducted over a span of more than 3 years. Dr. Roth's affidavit described the data he used as the "next best thing" and the "best available comparison".

[64] Dr. Roth then dealt with the issue of combining within his racemic average the results of assays that were conducted differently. Four of those assays were run starting with racemic lactone while the fifth was run with purified racemic sodium salt. Dr. Roth was not concerned by this because the lactone rings were treated to open and create the sodium salt *in situ*, albeit that no tests were run by Pfizer to determine whether this conversion was successfully accomplished.

[65] Dr Keana was highly critical of the CSI assays run by Pfizer and sceptical of the results they produced. He stated that it was not good practice to rely upon the results obtained from a single CSI assay or to average single assay values that span a broad range. The variability range of the CSI data relied upon by Dr. Roth was, according to Dr. Keana, unacceptably large. Of particular note is the significant variability between the measured activity level for the purified racemic sodium salt and the average of the four values obtained from the racemic lactone. At a minimum, this should have led Pfizer to doubt the validity of these assays.

[66] Dr. Keana also concluded that the data used by Dr. Roth was unreliable because of the reported inability of the laboratory technicians to create true solutions for the tested compounds. These solubility problems, he said, are reflected in the technicians' notes which used descriptors like "cloudy", "milky", "partially soluble" or "insoluble". These descriptors indicated that true solutions were not achieved for many of the tested compounds which would have led to unreliable results. Dr. Keana's affidavit described the problem as follows:

> 117. The point is that a single enantiomer may show greater than 2-fold increase in potency over the racemate simply because the racemate does not dissolve to the same extent as the single enantiomer and/or the racemate dissolves much slower from a suspension than the single enantiomer. An IC_{50} determination involves a reversible equilibrium. A racemate and the corresponding single enantiomer must be truly in solution in order to give a reliable IC_{50} value.

[67] According to Dr. Keana, these solubility problems could be aggravated by the well-known fact that significant solubility differences often exist between racemates and their corresponding enantiomers. Where only partial solubility is achieved for one or both of the comparators, the relative activity levels can be rendered meaningless. This point is made in the following passage from Dr. Keana's affidavit:

> 146. The point is that a single enantiomer may show greater than 2-fold increase in potency over the racemate simply because the racemate does not dissolve to the same extent as the single enantiomer. That is, the opalescent or milky stock "solution" of the racemate is *not* a solution at all. Such mixtures are *not* true solutions even if they do not evidence "gross lumps". The opalescence or milky nature is a result of light dispersion by small, likely colloidal particles. In such instances, a single enantiomer may well show a

> many-fold increase in potency over the racemate (even when the other enantiomer has no activity) simply because the racemate has dissolved to a lesser extent than the single enantiomer. A racemate and the corresponding single enantiomer must be truly in solution in order to give a reliable IC_{50} value.

[68] These criticisms by Dr. Keana are well-founded. Even if one were to accept at face value the hearsay evidence of the laboratory technician who conducted the CSI assays that she used the term "insoluble" to describe uniform suspensions of test compounds, the other problems identified by Dr. Keana remain. While visual distinctions of the sort made by Pfizer's laboratory technicians may well be commercially defensible, the practice is insufficient to support any valid scientific conclusion.

[69] Dr. Langer expressed similar concerns to those of Dr. Keana. He also questioned the appropriateness of Dr. Roth's averaging of assay data where four of the compounds tested were racemic lactones (where the lactone would presumably convert to sodium salt form *in situ*) and one compound began in a highly purified sodium salt form. Dr. Langer noted that the *in situ* conversion requirement introduced an element of potential experimental error into four of the five assays that was not controlled by measuring for lactone conversion. Dr. Langer gave an example from the Pfizer data which demonstrated his concern:

> 209. Similarly, utilizing the CSI activity data shown in Exhibit H of the May 22, 2006 Newton Affidavit, a direct comparison can also be made between the activities of the lactone forms of the R-trans enantiomer and the racemic mixture corresponding to atorvastatin. Using the results of CSI 107 for a direct comparison of the activities of the R-trans lactone form (as shown in Exhibit H from the May 22,

> 2006 Newton Affidavit, CSI 107 is the only assay for which data was obtained from the R-trans lactone form corresponding to atorvastatin) versus the results of CSI 92, 93, 95 and 102 (i.e., the four assays conducted utilizing the racemic lactone form that were averaged with the results of CSI 118 by Dr. Roth as described above) for the racemic lactone form results in an IC_{50} of 0.0355 micromoles/liter for the R-trans lactone compared to an average IC_{50} of 0.0541 for the racemic lactone form. This results in the calculation of an activity ratio of 1.52, indicating that the activity of the atorvastatin sodium converted in situ from the lactone form was demonstrated to be less than twice that of the racemic form.

[70] Dr. Newton's explanation for the absence of a test for assessing conversion was that in the drug discovery phase it would have taken too much time and would have "slowed discovery terribly to do that". This speaks again to the problem of relying for patent purposes on data that was generated under testing protocols that were constrained by commercial and other legitimate pragmatic considerations. Such considerations do not somehow improve the reliability of the data and are no excuse for declining to conduct appropriate scientific research at the stage of pursuing a patent.

[71] Dr. Langer also noted that if Dr. Roth had used for his comparison only the data from CSI 118 for the racemic sodium salt, he would have found only a two-fold advantage. This point was also made by Dr. Grieco who was of the view that the CSI 118 sodium assay produced the best available evidence to assess the activity level of the racemate. While I accept that relying only on the data from a single assay (CSI 118) would have presented its own set of problems, this disagreement by the experts illustrates that scientific conclusions

can be easily manipulated by the simple process of selecting data for comparison. This phenomenon is well-captured by the scientific truism that if one tortures the data long enough it will eventually confess.

[72] Dr. Dietschy's evidence was also qualified by issues of commercial practicality. For instance, in discussing the solubility issue, he stated that "the companies that work with these compounds are going to be starting out with a uniform suspension". He noted that solubility difficulties were common in the testing of statins and that this could generally be overcome by using solubilising agents. Dr. Dietschy also excused Pfizer's practice of not measuring the concentration of test compounds because to do so would be incredibly expensive, difficult and tedious from a practical standpoint. His testimony suggested that commercial practicality could trump scientific rigour where an innovator is simply attempting to screen compounds for further development:

> A. I think that's the way you assume it's going to go when you do these initial assays. The company is looking for guidance about which compounds are going to be useful and which ones are reactors.
>
> Q. So why are you going to assume different compounds are going to dissolve in the same way?
>
> A. Well, I didn't say that. I said that two isomers, for example, and S and an R isomer might have similar degrees of dispersion in dissolution.
>
> Q. They might not?
>
> A. They might not.
>
> …

> Q. And am I right that the point of doing assays like the CSI and the COR, the point of doing those is to get meaningful information about a compound?
>
> A. I think it's a little different than that. In a drug discovery program what you are attempting to do is to sort out of the many compounds that the organic synthetic chemists have made, which might have unusual activity that you can then pursue with more complex and expensive tests. For example, going in vivo. So it's not just looking at the potential effectiveness of those, but rather to select out of a number of compounds which are the most promising.
>
> [Emphasis added]

[73] While there is merit to Dr. Dietschy's observations in a commercial context, they are far less compelling in a scientific context and when evidence is being assembled to support a patent application. On this fundamental point, I agree with Dr. Grieco's view expressed at para. 196 of his affidavit where he stated:

> Dr. Dietschy basically knows that it is very important to know concentrations of test compounds in stock solutions. It is sad that he makes the comment that "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". I cannot agree with his statement. I am of the strongest belief, as in the present case, that once a drug candidate had been discovered and the time has come to disclose the invention in a patent application, it is of outmost importance to determine the actual activity of the racemate and the two enantiomerically pure forms of the racemate regardless of expense and time. […]

[74] The same point is made by Dr. Langer at para. 182 of his affidavit:

> […] The Pfizer Experts repeatedly point to this variability as the justification for their apparent focusing on the results from the CSI 118 assay as the sole "head-to-head" demonstration of the purported "unexpected and surprising" activity of atorvastatin calcium. However, in my opinion, such variability would indicate to me as a scientist that one single data point from a body of data should not be selectively considered after generation of the data (i.e., "after the fact") as the sole valid data point, in particular where significant experimental errors are associated with part of this body of data (as for the data generated via the COR and CSI assays as I discuss below). Instead, controlled experiments should be designed and conducted in an unbiased manner, with individual experiments repeated enough times to allow for statistical analysis to be performed on the data. Such designs could still include "head-to-head" experiments; these would simply be repeated in the manner described above.

[75] Dr. Dietschy's opinions were based on some other assumptions that were not well founded. The most significant of those was his assumption that all of the tested compounds had been prepared to the point at least of uniform suspension. This was based on what he had been told including hearsay obtained by Dr. Newton from the responsible laboratory technician. She ostensibly told Dr. Newton that she had used the term "insoluble" to describe "uniform suspensions" and that even after 18 years she could confirm that all of the subject assays achieved that state. Dr. Newton's affidavit does not disclose what she meant by the terms "cloudy", "milky" or "partly soluble".

[76] This hearsay evidence is particularly troubling because it is fundamentally important to the opinions offered by Pfizer's experts and should have been supported by an affidavit from the responsible laboratory technician. It is very difficult to accept at face value that the term "insoluble" was intended to describe a uniform solution, particularly where a number of other more synonymous terms appear in the technician's notes.

[77] The apparent absurdity of Dr. Dietschy's working assumption on this point is reflected in a number of exchanges with counsel including the following:

> Q. So they tried to get it to be soluble, but it doesn't seem to be soluble; is that correct?
>
> A. It is still not fully soluble.
>
> Q. What - - insoluble to you means not fully soluble? Pardon.
>
> A. Insoluble, as I understand her use of the word, is a milky solution or uniform suspension.
>
> Q. And you're getting that from a discussion that you read that someone else had with the technician?
>
> A. That's where I'm getting that interpretation.
>
> Q. So insoluble, according to that information, is partly soluble?
>
> A. Yes.
>
> …
>
> Q. All right. Let's go to 124488-15, the fourth item down. You see when - - when the Sonic and whatever else is done the technician writes: Milky, partly soluble?

A. Yes.

Q. Why is she writing that if the word "insoluble" means exactly that?

A. She may have been using the two terms synonymously. I have no idea why she switched.

[78] Dr. Dietschy's effort to gloss over Pfizer's inability to obtain pure test solutions is also evident in the difference between his evidence in this proceeding and his testimony in the United States. In the United States, he referred to this as a "solubility problem" but in this proceeding he only reluctantly adopted that description upon being confronted with his earlier evidence.

[79] Dr. Newton's attempt to justify his assumption of solubility was as tenuous as Dr. Dietschy's, as is reflected in the following passage from his testimony:

Q. Is there some legend that I could see within the company whereby the word "insoluble" equals uniform suspension? Is there a legend?

A. We did not have a legend, no.

Q. So there is no, like, dictionary for the word "insoluble"?

A. There is no gradation as far as what we considered the - - the terms that were used were "milky", "cloudy", "insoluble", "uniform suspension". Those were synonymous. It is how much light can actually pass through that particular suspension.

Q. What is the distinction between cloudy and milky? What does that mean?

A. It is in the eye of the beholder. It is in the eye of Erica Ferguson. Cloudy, obviously milk is thicker.

Q. Why do you say that?

A. It is more dense than cloudy.

Q. How do you know that is what she meant?

A. I am just guessing.

[80] Pfizer's reliance on hearsay evidence to interpret the obvious ambiguities and inconsistent language in the experimentation notes is, here again, inappropriate. This was important evidence which bore directly on the reliability of the assays Pfizer used to support its claim to a novel and surprising finding. Even Dr. Dietschy's testimony indicated that there was a risk of experimental error where the laboratory technician failed to obtain a uniform suspension for the tested compounds.

[81] Pfizer's failure to put forward an affidavit from the laboratory technician, or to explain why that could not be done, supports an inference that Dr. Dietschy's and Dr. Newton's solubility assumptions were invalid and that these assays were methodologically deficient: see Federal Courts Rule 81(2). Their willingness to assume that Pfizer's technicians followed sound laboratory practices is also undermined by the serious and admitted deficiencies that plagued its COR assays and by Pfizer's failure to require its laboratory technicians when describing their observations either to use consistent terminology or otherwise to define that terminology.

[82] The reliability of the CSI assays is further called into question by the fact that the responsible technicians ran assays to completion and recorded the data even when the mixtures were compromised by solubility problems that clearly exceeded Pfizer's testing standards. This problem was acknowledged by Dr. Newton in the following passage from his testimony:

> Q. The protocol was clear that in running a CSI screen, you were permitted to use a uniform solution?
>
> A. A solution.
>
> Q. A solution. You were not permitted to use something that was not such a solution, i.e., something which had chunks or flakes in it, correct?
>
> A. That is correct, and she went ahead and did it, anyway.
>
> Q. So she broke the protocol?
>
> A. Which is what she shouldn't have done.
>
> Q. So she violated the protocol.
>
> A. According to the research report, she should not have done the experiment.
>
> Q. So you will agree with me that she violated the protocol?
>
> A. She did not follow the protocol.

[83] Dr. Newton also appears to have expressed doubt about Dr. Roth's willingness to draw a conclusion about the efficacy of atorvastatin calcium from the CSI data on atorvastatin sodium. His testimony on this was as follows:

> Q. So from what you have just said, you wouldn't use the sodium salt to predict or evaluate the calcium salt?
>
> A. I would not.

This is an important issue because all of the data relied upon by Dr. Roth in the '546 Patent resulted from CSI assays of sodium salts and not of calcium salts.

[84] In the end, neither Dr. Dietschy nor Dr. Newton fully endorsed Dr. Roth's approach to the CSI data. Dr. Dietschy's affidavit described CSI 118 (testing the calcium salt) as "the only valid (i.e., head-to-head) comparison" of the racemic mixture and its two enantiomers and in testimony he distanced himself from the data relied upon by Dr. Roth for the following reasons:

> Q. So, essentially, just to recap, the rasimate [sic] is an average of five values. The other two values appear to come from CSI 120?
>
> A. That's correct.
>
> Q. Thank you.
>
> A. That's my understanding.
>
> Q. And, in general, you would agree that taking an average across different days and experiments is not something that you would you?
>
> A. No. I - - had I been there, I would not have done it exactly that way.

[85] Dr. Newton similarly took issue with Dr. Roth's use of the CSI data as is reflected in the following passage from his testimony:

> Q. Let me ask you this question. Would you agree that in comparing various compounds to report the results, it was not proper to compare across CSI experiments?
>
> MR. WILCOX: To report results where?
>
> BY MR. RADOMSKI:
>
> Q. In the patent.
>
> A. I have no idea what would be required for the patent, because I had nothing to do with the patent.
>
> Q. But in terms of presenting data and comparing results of enantiomers to racemates, do you agree that it was not proper to compare across CSI experiments?
>
> A. That is not the way I would have done it. I would have it in the same experiment. But I don't know the conditions or situation, or why Bruce made the decision that he made, because it was not involved in any of this work related to the patent.
>
> Q. So in terms of taking an average for the racemate and presenting a value for racemate which is the average of five different values, I take it that is not something you would have done to present the value of the racemate?
>
> A. I think I just stated that.

[86] Given the quality-control issues that were associated with Pfizer's compound screening processes and the obvious weaknesses in the data they produced, it is surprising that Pfizer relied upon that information at all to support the '546 Patent claims. At the stage of looking for defensible evidence to support inventiveness, it would not have been difficult

for Pfizer to have conducted some discrete and well-controlled assays of atorvastatin to obtain reliable data. Instead, Dr. Roth selected suspect data to support a dubious claim of a ten-fold advantage. Having regard to all of the evidence, I am prepared to draw an inference that Pfizer did not conduct further experimentation because it believed that well-controlled assays would not support its assertion of a surprising and unexpected finding for atorvastatin.

[87] On the basis of the foregoing, I reject unequivocally the reliability of the data selected by Dr. Roth and relied upon by Pfizer to support the claim of a ten-fold advantage for atorvastatin calcium.

The COR Assays

[88] Dr. Dietschy attempted in his initial affidavit to use Pfizer's COR assay data to support his opinion that the atorvastatin enantiomer exhibited "an unexpectedly high degree of inhibitory activity" compared to the racemic mixture. He asserted that he had reviewed the laboratory notebooks and was satisfied that the data were accurately reported. He went on to state that the COR data came from "good head-to-head comparisons performed under good experimental conditions". From one of the COR comparisons, he observed that atorvastatin calcium was unexpectedly found to be 3.5 times more active than the racemate. From another of the COR assays, he found that the atorvastatin calcium was about 6 times more active than the racemate. Both of these, he said, were surprising.

[89] This evidence from Dr. Dietschy was similar to the initial evidence given by Dr. Newton. Dr. Newton was largely responsible for the development of Pfizer's COR analysis and he acknowledged that during the drug discovery phase the COR screens were carried out by laboratory technicians at his request and under his supervision. His initial review of the COR assay data also led him to conclude that the results were surprising and unexpected inasmuch as they indicated a heightened level of activity for atorvastatin over the racemate of between 3.5 and 6.2.

[90] Dr. Newton later claimed to have determined that the COR data had been incorrectly graphed and the values miscalculated by one of the laboratory technicians. In his supplementary affidavit, he restated the COR values for atorvastatin calcium in a range between 1.53 and 3.3, producing an average of 2.41. This, of course, is well below the ten-fold increase reported in the '546 Patent. It is also well below the COR range initially reported by Dr. Newton and by Dr. Dietschy and is close to the anticipated value of a two-fold increase in efficacy.

[91] Dr. Newton went on to resile completely from the COR data by declaring it to be unreliable. He claimed that the revised values were too variable to be trusted. Dr. Newton also relied upon hearsay evidence ostensibly obtained by him from the laboratory technician responsible for the COR assays. He attributed statements to the technician that she had made a number of methodological mistakes in carrying out her COR analysis. These, he deposed, would have had an effect on the COR data thereby rendering that data unreliable.

[92] Dr. Newton's attempt to use hearsay evidence in this manner is completely unacceptable and this evidence is inadmissible. If the responsible laboratory technician was available to speak to Dr. Newton, she was presumably available to swear an affidavit which acknowledged the mistakes attributed to her along with their significance, if any, to the reported COR data. The statements attributed to her by Dr. Newton lacked specificity with respect to the subject COR assays and are nothing more than generalizations about the laboratory technician's research practices, supposedly recalled after 18 years. Those statements are so lacking in quantitative and qualitative detail that they cannot support Dr. Dietschy's and Dr. Newton's opinions that the COR data was rendered unusable. Pfizer's failure to produce an affidavit from the responsible laboratory technician and to thereby open up the possibility of a cross-examination on this important evidence leads me to draw an adverse inference and to conclude that Dr. Newton, at a minimum, overstated the significance of what he was allegedly told.

[93] Dr. Dietschy also later retreated from any reliance on the COR assay data when he was told that the COR research was apparently badly performed. He asserted that the supposed weaknesses in methodology caused him to lose confidence in the reported data. His supplementary affidavit asserted that the variability of the results of the COR assay also made them unreliable.

[94] The concerns expressed by Dr. Dietschy and by Dr. Newton about variability are strange. In his initial affidavit, Dr. Dietschy stated that there is an inherent variability in the results obtained from CSI and COR assays. To the same effect was the following affidavit evidence from Dr. Newton:

> 62. In the drug discovery process, the atherosclerosis drug discovery team was most interested in *relative* IC_{50} values. We wanted to rank order the test compounds according to their potency in each assay. Because the CSI and COR assays were biological systems subject to inherent variability from various sources, we never considered the IC_{50} values to be absolute.
>
> 63. The IC_{50} values of compactin were not the same each time the CSI or COR screen was run because of the inherent variability when such assays are run.
>
> 64. Reasons for the variability in the IC_{50} values between runs of the *in vitro* assays on different days include the following:
>
> (a) animal-to-animal variation in the amount of HMG-CoA reductase present in the liver of each rat used in the experiment, and therefore in the whole-liver homogenate prepared on a given day;
>
> (b) age of the microsomal preparation being used;
>
> (c) the test compounds being solubilised to different extents; and
>
> (d) human error in carrying out the procedure as set out in the protocol (e.g., dilution errors and errors in pipetting).

[95] These early acceptances by Dr. Dietschy and Dr. Newton of the variability in COR values in a range between 3.5 and 6.2 are inconsistent with their later attempts to dismiss the

COR data when it was adjusted and found to reflect values of only an approximate two-fold increase in the efficacy of atorvastatin over the racemate. This adjusted range of efficacy for atorvastatin is no more profound than the earlier range that they were both willing to accept as reliable when it supported their opinions.

[96] Dr. Newton's attempt to undermine the validity of the COR data is particularly troubling in the face of his initial evidence that he had reviewed the data and found it to be reliable. To the extent that any mistakes that Dr. Newton now attributes to the laboratory technician were apparent in Pfizer's records, this reflects poorly on the adequacy of Dr. Newton's initial review of the COR data and completely undermines Dr. Dietschy's initial statement that the COR tests "were performed under good experimental conditions".

[97] It is apparent that the Pfizer witnesses were throughout inconsistent about the quantitative utility of the COR data. Dr. Roth's initial search for surprising and unexpected assay values did not include a review of the available COR data because he said that Pfizer used that test only for the validation screening of compounds. However, when it was thought that the COR data might lend support to Dr. Roth's quantitative analysis, the Pfizer witnesses sought to rely upon it. Later when those data were adjusted and they pointed away from a surprising and unexpected result, those same witnesses rejected the data as unreliable and too variable. This inconsistency undermines the credibility of Dr. Dietschy and Dr. Newton and is strongly suggestive of a lack of objectivity. While there were undoubtedly some weaknesses in the COR data, that data did indicate that Dr. Roth's

adoption and interpretation of the CSI data were suspect. The fact that Pfizer used the COR assay for generic screening purposes does not provide an empirical explanation for Dr. Roth's failure to examine the data it produced. This is supported by the willingness of Dr. Newton and Dr. Dietschy to rely upon the COR results when those results suited their purposes.

The Atorvastatin Calcium Head-To-Head Assay (CSI 118)

[98] The primary foundation for Pfizer's present claim for the surprising and unexpected activity of atorvastatin calcium is data obtained from CSI calcium assay 118 located by Dr. Roth only after the '546 Patent application was filed. That data did indicate that atorvastatin calcium had approximately ten times more activity than the racemate. Dr. Roth's affidavit described the discovery of this data as follows:

> 148. Some time later I was asked to prepare a declaration for filing in the 995 Patent application. I returned to the data in the binder maintained by the Chemical Coordinator to again review the data. At that time, I found a head-to-head comparison of the racemate, the R-trans enantiomer and the S-trans enantiomer all tested as a calcium salt in the same experiment. I do not know to this day why I did not see this head-to-head data during my initial review of the binder, but I know I did not see it at the time. This was surprising because it was, and is, exactly what I was looking for - - that is, the best possible data: all three compounds were tested head-to-head as the calcium salt in the same assay. The data from this head-to-head comparison is attached as Exhibit "G".

[99] I have reservations about the legal propriety of permitting a patentee to rely upon after-obtained evidence to support a previous selection. If the information used to support

the patent application did not establish inventiveness at the time, it is difficult to accept that inventiveness can be established retroactively. This problem was noted briefly by Lord Reid in *May and Baker Ltd. et al. v. Boots Pure Drug Company Limited* (1950), 67 R.P.C. 23 at page 57 where he said:

> There is a good reason why a patentee should not be allowed to introduce a new selection by amendment: the new selection may be based on knowledge which he has only recently acquired and if it were allowed he would be able to claim something which he had not invented when he got his patent.

[100] The difference, perhaps, in this case, is that the subsequently identified evidence relied upon by Pfizer was apparently in existence at the time of its patent application but no one had found it. That is probably a sufficient distinction to allow Pfizer to rely upon the evidence later, albeit that it does not eliminate the more prosaic concern that Dr. Roth's initial data search was not particularly thorough.

[101] Nevertheless, Pfizer's reliance on the data produced by this assay is unfounded for many of the reasons previously canvassed. As with Pfizer's other assays, the technician's notes for CSI 118 indicate that there were solubility problems associated with the tested compounds. Those notes stated:

> […] PD 124,488-38A (Racemic hemi Ca salt). An entry in Appendix I of the Newton Affidavit, under CSI #118 dated 10/24/88 indicates "insol KOH sonic + HB warm insol"
>
> PD 134,298-38A (atorvastatin hemi Ca salt). An entry in Appendix I of the Newton Affidavit, under CSI #118 dated 10/24/88 indicates "insol KOH sonic + HB, warm insol"

[102] I am not prepared to accept that the above-noted reference to "insol" meant that the compounds tested had reached a state of uniform suspension. The only obvious conclusion to take from the technician's notes is that, notwithstanding steps to obtain solutions (eg. sonication and warming), the compounds were not fully solubilised. Despite having being subjected to several processes, the compounds, which began as "insoluble" remained "insoluble".

[103] The validity of this assay depended, at a minimum, on the assumption that the compounds tested had reached a state of uniform suspension or, in the words of Dr. Dietschy, "were equally soluble". This is an unsafe assumption because it was based upon unreliable and untested hearsay and because it is generally inconsistent with the terminology used throughout by Pfizer's laboratory technicians. Furthermore, while it may have been commercially acceptable to rely upon the subjective visual observations of technicians to assess the solubility of tested compounds, I accept the evidence of the Apotex witnesses that that practice is unreliable from a scientific perspective. The weakness of that practice could have been overcome had Pfizer taken steps to measure the concentration of the tested compounds but, presumably for commercial reasons, it did not do so.

[104] I would add that Pfizer's practice of running assays to completion even when its own solubility standards were not met further undermines the working assumption made by Pfizer's experts that the methodology of CSI 118 is unimpeachable. I would add to this that

the almost unwavering reliance by Pfizer's experts on the reliability of the CSI 118 assay is considerably at odds with the evidence that its assay practices were plagued by quality control problems (eg. the COR assays) and that its testing protocols were driven by commercial and not scientific motivations.

[105] There is also circumstantial evidence that the CSI 118 assay of racemic calcium produced data of doubtful validity. In theory, the activity level for racemic sodium salt and for racemic calcium salt as measured by CSI 118 should have been roughly equivalent. While some variability could be expected, the approximate ten-fold variance between those values ought to have raised a concern in the minds of Pfizer's analysts that something was wrong with the assay. Here I accept the evidence of Dr. Grieco and Dr. Langer over that of Dr. Dietschy. According to Dr. Langer this "extensive variability" between the calcium and sodium salt forms could be attributed to the poor solubility of the compounds, differing dissolution rates, the extent of particle size distribution and time factors, all of which create areas for significant error.

[106] The final point of concern with respect to the CSI 118 calcium salt assay is that, sitting by itself in a sea of methodological problems, it cannot and does not support any conclusion about the relative efficacy of atorvastatin calcium over the racemate. On this issue, I adopt the common sense evidence of Dr. Langer as expressed in the following passage from his affidavit:

> 213. I disagree with the Pfizer Experts on this point. Again, in light of all of the issues, errors, and concerns

> associated with both the COR and CSI data related to this matter, I disagree with the allegation that essentially only a single assay, that being CSI 118, should be considered as proof of the "unexpected and surprising" activity of atorvastatin calcium in comparison to the racemate. In my opinion, given the abovementioned issues with the experimental procedures and *in vitro* data related to this matter, one single assay cannot and should not be relied upon to make any quantitative conclusions with respect to the relative activity of atorvastatin calcium compared to the racemate. Good scientific practices call for experimental results to be validated by performing repeats of experiments to determine that quantitative differences in the activity of compounds under study are statistically significant. This is even more important for experimental assays that are associated with (i) increased levels of variability due to the use of biological systems, etc. (as in repeatedly noted to be the case for the CSI assay by the Pfizer Experts as described above) and (ii) significant levels of experimental operator error (as also appears to be the case for this matter as described above). Thus, in my opinion, the results of the single CSI 118 assay should not be relied upon as the sole purported proof of the "unexpected and surprising" activity of atorvastatin calcium, particularly in light of the fact that, as described above, much of the additional *in vitro* CSI and COR data that has been discounted by the Pfizer Experts as described above appears to contradict the results of CSI 118.

[107] Even Dr. Dietschy admitted under cross-examination that this assay produced only "a factual finding of some considerable interest". He also conceded that without the assay being repeated a sufficient number of times, its statistical significance could not be ascertained. Here, he returned to the issue of commercial practicality to justify Pfizer's use of a single assay result:

> Q. That's not the question. The question is that whether - - the fact that someone might choose to use the result or act upon the result doesn't necessarily mean that the result is true in the sense I'm using it. The

only way to determine truth, in fact, is to run a number of experiments and establish statistical significance?

A. That would be helpful if you're going to stop with that result. But, again, one has to reasonably look at what was being done here.

In discovery programs it is very common to move fast against the competition and to pick out those results which suggest compounds may be of great interest and should be pursued. That may be done without necessarily repeating the experiment 100 times or 50 times to get a mean and a standard error.

So I accept the first part of your statement. I'm saying that's not necessarily how things work.

[108] When Dr. Dietschy was brought back to the issue of good scientific practice, he offered the following testimony:

Q. I'm not asking you about the patentability or the proper writing of a patent, I'm asking you as a scientist. The results on Page 8 at the moment they were obtained as a scientist, take a snapshot at that moment, not what you learned later on when it goes into humans or animal models or whatever else, just at that moment in time, you get the data that's shown on Page 8, as a scientist you could not attach truth, in the sense that I'm using it, because there's no statistical significance that was performed or could have been performed on that data.

A. You would have liked to have done it over and over again for that reason.

Q. Okay. Thank you. Just in relation to the data in the patent on Page 8 and the notion of ten-fold, am I right that ten-fold activity of Atorvastatin over rasimate [sic] was not observed either in COR uncorrected, corrected, or AICS – AICS?

A. Not ten-fold, but - -

Q. That was the question, ten. It was not observed in those experiments?

A. No, not ten-fold, but it was elevated above two-fold in most of those.

Q. Okay. And ten-fold result in the patent is not from a single experiment, I think we've established that, correct?

A. That's correct.

Q. And the only ten-fold result in a single experiment that you can point to is CSI 118?

A. That's correct.

Q. And that's the only time you've seen a ten-fold result in that single experiment, of all the data you've looked at, correct?

A. That's correct.

Q. You cannot calculate - - and I may have asked you this again and I apologize - - the error associated with that result?

A. No, I can't.

Q. And, therefore, can't say that it's statistically significant or not, correct?

A. Correct.

[109] For the reasons stated above, I do not accept Pfizer's assertions that the data obtained from CSI 118 gave a valid indication that atorvastatin calcium was surprisingly or

unexpectedly more efficacious than the racemate. I find instead that that assay was unreliable and the data it produced scientifically invalid.

AICS Assays

[110] As previously noted, Pfizer subjected atorvastatin calcium to *in vivo* testing in the form of AICS assays. The AICS data came from well-controlled animal studies and established that atorvastatin calcium was approximately two times more active in inhibiting cholesterol synthesis *in vivo* than the racemate. This conclusion is confirmed in two confidential research reports prepared by Pfizer respectively on May 31, 1989 and January 4, 1990 and it is not the subject of any present disagreement. Indeed, Dr. Dietschy described the AICS assays as "strong studies".

[111] While I accept Pfizer's point that the AICS *in vivo* data do not disprove the supposed results of Pfizer's *in vitro* experiments, those data were certainly in keeping with the expected two-fold advantage of atorvastatin and, therefore, cast considerable doubt upon the reliability of Pfizer's *in vitro* work. Pfizer knew when it submitted the '546 Patent application that there was no unexpected *in vivo* advantage to be had with atorvastatin calcium and Pfizer's selective reliance on suspect *in vitro* data to support the promise of the Patent was, in the face of all of the available data, disingenuous.

[112] I also do not accept Dr. Dietschy's opinion that the AICS results should not be used for drawing quantitative comparative conclusions about the inhibitory effects of atorvastatin

calcium *in vivo*. Pfizer used the AICS assays precisely for that purpose and so did Drs. Roth and Newton. In a product profile co-authored by Drs. Roth and Newton in June 1989, it was stated unequivocally on the strength of the AICS experiments that "the purified enantiomer atorvastatin had been shown to be two times more potent than the racemic drug". I would add that Dr. Roth's attempt in testimony to distance himself from that statement was implausible and further damaged his credibility in this case[1].

Salt Selection

[113] Pfizer maintains that the '546 Patent contains a second inventive selection involving the choice of calcium as the preferred salt for its medicinal formulation of atorvastatin. Pfizer says that salt selection is a complex and unpredictable process involving more than routine experimentation. The choice of a salt is dependent upon a number of physical properties including chemical stability, solubility, hygroscopicity and processability, none of which can be easily predicted. In the case of atorvastatin, Pfizer determined that the hemicalcium salt was the preferred embodiment of the atorvastatin compound. Dr. Roth's affidavit summed up Pfizer's research around the choice of calcium in the following passage from his affidavit:

> 135. At the time I initiated the work that resulted in the selection of calcium as the salt, I had no expectation as to which salt would be most preferable. The literature was of little help: most of the statins that had been reported in the art were reported as sodium salts. It was unexpected that the calcium salt of atorvastatin would have the best set of properties. In light of the problems that we encountered with

[1] Dr. Roth testified: «That statement was in there. It doesn't mean that it's an accurate statement or one that I wrote or agreed with».

> the sodium salt, it was not obvious which salt would be preferred. The selection of calcium, however, was based on our internal testing.

[114] Apotex argues that there is nothing in the '546 Patent which supports Pfizer's claim to an inventive selection of calcium over the other salt formulations it tested. Apotex points out that Pfizer included calcium in a routine screening study along with six other salts and concluded only that "the most preferred embodiment of the present invention is…[atorvastatin] hemicalcium salt". According to Apotex, the Patent fails to disclose any special advantage achieved by the use of calcium over the other possible salt formulations and it contains no information as to why calcium is better than the other choices. The idea that Pfizer's choice of calcium constituted a valid selection over other salt forms is inconsistent with the inclusion of sodium, potassium, methylglucamine, magnesium and zinc in other claims of the '546 Patent. According to Apotex, there was no selection of calcium over the other salt forms claimed.

[115] While I accept Pfizer's point that the choice of a salt in the preparation of a medicinal formulation may be inventive and, therefore, can constitute a patentable selection, it is clear from the authorities that the discovered special advantage must be adequately disclosed. In the context of the claims advanced by Pfizer in the '546 Patent, I have concluded that its disclosure does not meet the standards set by the leading authority of *Farbenindustrie*, above. There Justice Maugham held that a valid selection requires more than a bare assertion of "advantages"; what is required is a clear description of the special

advantage or characteristic that supports the choice made over the other members of the class. The same point was recently made by Justice Roger Hughes in *Eli Lilly Canada Inc. v. Novopharm Ltd.*, 2007 FC 596, 58 C.P.R. (4th) 214 where, after a thorough review of the authorities, he held:

> 162 I find that the '113 patent fails to provide sufficient disclosure in its specification as to the invention, if any, in selecting olanzapine from a previously disclosed group of compounds. The prior art British Patents says that the whole class of compounds to be useful in treating central nervous system disorders. The invention in selecting olanzapine is the so called "surprising and unexpected" properties of olanzapine in "comparison with flumezapine and other related compounds". No such comparison is made anywhere in the '113 patent. No data was given. We are left only with rhetoric such as "high level of efficiency" and "mild and transient" and "lower" side effects. The puzzling and scant mention of a dog study refers only to ethyl olanzapine and tells nothing of flumezapine or other compounds.

[116] I do not accept that the assertion that atorvastatin calcium is the preferred medicinal embodiment meets the required standard of disclosure, particularly in the context of claims in the '546 Patent over several other salt formulations and where the Patent recognizes the general equivalency of all of the salt formulations in reducing cholesterol levels (see page 9 at line 5). The fact that Pfizer has claimed several different salts for atorvastatin suggests that there was nothing particularly special about calcium. Even if there was, Pfizer had an obligation to disclose that advantage in order to support a claim of selection and it made no such disclosure. Furthermore, in such a context, the statement of a simple preference is not a selection at all. Support for this can be found in *Whirlpool Corp. v. Camco Inc.*, 2000 SCC 67, [2000] 2 S.C.R. 1067, at para. 54 where Justice Ian Binnie, writing for the Court,

stated that a "preferred embodiment" is not exhaustive of an invention but only one example of it.

[117] With respect to the issue of the sufficiency of Pfizer's disclosure, I would note that Justice Konrad von Finckenstein reached the same conclusion in *Pfizer Canada Inc. v. Canada*, 2006 FC 1471, 54 C.P.R. (4th) 279. Even if I had had some reservation about the resolution of this point - and I do not - it seems to me that, absent manifest error or severe injustice, I am bound by the principle of comity to follow Justice von Finckenstein's decision. This is, after all, an issue of legal interpretation for which a consistent resolution should be expected.

[118] Even if I am wrong about the adequacy of Pfizer's disclosure, I am not satisfied that its choice of calcium as its preferred medicinal embodiment was achieved by anything inventive. The evidence before me establishes that the choice of calcium was made on the basis of routine and limited salt screening, the conclusion of which post-dated the priority date of the '546 Patent. This is inconsistent with Pfizer's position that the preference for calcium was a selection. As previously noted, a finding which post-dates the priority date of a patent cannot be the basis of an assertion of earlier inventiveness.

Commercial Success

[119] There is no doubt that LIPITOR has been a hugely successful product for Pfizer. That success may well have been largely dependant upon its treatment advantages but, in the

context of a claimed selection invention, I do not see how commercial success can be relevant. Pfizer had already obtained a product patent over atorvastatin in its '893 Patent. If this proceeding had involved a challenge to the '893 Patent, the relative success of LIPITOR over the competing statin products could have been a relevant, albeit secondary, consideration. However, the fact that atorvastatin calcium may well be a better cholesterol inhibitor than the competing products does not assist in determining whether it has unexpected advantages over the class from which it was chosen. With respect to that issue, commercial success has no relevance.

Conclusion (Selection)

[120] For all of the reasons given above, I do not accept Pfizer's evidence that atorvastatin has an unexpected or surprising inhibitory advantage over the racemate. The assay data relied upon by Pfizer in this case are wholly unreliable and failed to establish any level of activity for atorvastatin beyond what a person skilled in the art would have expected to see, that is, no more than a two-fold advantage. I also do not accept that Pfizer's choice of calcium as the preferred salt form for atorvastatin represents a valid selection. It necessarily follows that the '546 Patent is invalid because it does not meet the test for a valid selection and because it is objectionable for claiming subject matter already monopolized by the '893 Patent.

Costs

[121] The costs of this application are payable to Apotex. I will allow the parties 10 days to make submissions with respect to the quantum of costs payable.

" R. L. Barnes "
Judge

FEDERAL COURT

NAME OF COUNSEL AND SOLICITORS OF RECORD

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