Federal Court  Cour fédérale

Date: 20100917

Docket: T-1610-08

Citation: 2010 FC 933

Ottawa, Ontario, September 17, 2010

PRESENT: The Honourable Mr. Justice Phelan

BETWEEN:

MERCK-FROSST - SCHERING PHARMA GP and SCHERING CORPORATION

Applicants

and

THE MINISTER OF HEALTH and TEVA CANADA LIMITED

Respondents

REASONS FOR JUDGMENT AND JUDGMENT

I. INTRODUCTION

[1] This is an application pursuant to s. 55.2(4) of the *Patent Act* and s. 6 of the *Patented Medicines (Notice of Compliance) Regulations* (SOR/93-133) by Merck-Frosst – Schering Pharma GP and Schering Corporation (Merck) for an order prohibiting the Minister of Health from issuing a Notice of Compliance (NOC) to Novopharm Limited for its generic version of the drug Ezetimibe.

[2] Novopharm Limited is now known as Teva Canada Limited, an order changing the style of cause has been issued.

[3] Ezetimibe is a drug used in the treatment of cholesterol and is covered by Canadian Patent 2,172,149 (the '149 Patent). It is a hydroxyl-substituted beta-lactum compound which was discovered after further research on a previous patent, Canadian Patent 2,114,007 (the '007 Patent) for hypocholesterolemic beta-lactum compounds.

[4] Teva alleges that the '149 Patent is obvious in light of the '007 Patent. Its principal witness, Dr. Sutherland, set out a “ten step” process which he claimed a “person of ordinary skill in the art” (POSITA) would have known to follow and which would have led easily and without difficulty to the '149 Patent.

[5] Teva’s evidence stands in marked contrast to what actually happened in the discovery of Ezetimibe and in marked contrast to Merck’s expert witnesses’ testimony as to what a POSITA would know about how “easily” Ezetimibe could be discovered.

[6] The central issue in this case is a stark choice between experts as to whether the '007 Patent made it “obvious to try” what became the '149 Patent set against the reality of what Merck did to discover Ezetimibe.

II. BACKGROUND

A. *Preliminary*

[7] Ezetimibe is used for the prevention and treatment of cardiovascular disease atherosclerosis which occurs when cholesterol and other substances build up in the artery walls. This condition leads to heart attack, stroke and possible death. The key to treatment and prevention is lowering cholesterol levels.

[8] As outlined in the '149 Patent, “cholesterol esters” are a major component of the lesions which build up on artery walls. They play a role in the intestinal absorption of cholesterol. Inhibiting the formation of these esters and reducing cholesterol serums is a means to lowering cholesterol and inhibiting the formation of lesions.

[9] The liver is a prime determinate of plasma cholesterol levels at the site of synthesis and the secretion of very low density lipoproteins (VLDL) which are metabolized into low density lipoproteins (LDL). LDL carry cholesterol in the plasma and an increase in their concentration correlates to increased risk of atherosclerosis. If less cholesterol is absorbed, less VLDLs are created with the net effect of reducing plasma cholesterol levels.

[10] The usual drug employed to treat atherosclerosis was and continues to be statins. The Respondent’s unchallenged evidence is statins continue to dominate this field, although, as noted by the Applicants, this drug displays side effects rendering some patients “statin intolerant”.

Merck developed Ezetimibe in an effort to provide an alternative or complimentary drug option.

[11] Ezetimibe is a type of beta-lactum which is a synonym for azetidinone. Beta-lactums are rings on which one can position substituents (parts of molecules) in a characteristic and spatially defined way.

[12] There was considerable expert debate about “biotransformation” and “metabolism”. Biotransformation is the chemical mediation made by an organism on a chemical compound – drug metabolism in the body is an example. Metabolism results in metabolites or putative metabolites (metabolites expected to exist but not yet tested) which are the transformed compounds.

[13] The expert evidence was consistent that there are two stages of metabolism. Phase I metabolism creates metabolites which can be active biologically, less active or of different activity from the parent compound.

Many Phase I metabolites are then susceptible to Phase II metabolism which normally rids the products from the body usually through excretion – not always with a drug. The Phase II metabolites are likely to be inactive. The likelihood of Phase II metabolism and the ability of compounds to revert to Phase I metabolism was an area of considerable contention between opposing experts.

[14] Throughout the expert evidence there was reference to the “Lock and Key” phenomenon. In order to have an effect, a drug molecule binds with the target in the body. The shape of the molecule and its electronic properties will affect the interaction. There are multiple points of contact between the “key” (the molecule) and the lock (the target) so that changes in either can affect the way a drug binds to the target.

[15] A key aspect of Teva’s sole expert opinion by Dr. Sutherland is “oxidated metabolism” or “oxidation”. This is a type of biotransformation which results in Phase I metabolism. Oxidation is part of the process by which hydroxyl groups (OH) can be added to a compound.

[16] The basis upon which Teva claims that a POSITA could easily attain the claimed invention based on the prior art involved “SAR Analysis” (structured activity relationship analysis). This is the type of analysis used to predict the effect of a drug or compound on the basis of its molecular structure.

[17] Scientists attempt to discern how the activity of a compound is changed by small changes to its structure. Therefore, only a single change can be made at any one time so that the effect of the change can be tested. Analogues (molecules with slight differences but a similar structure to known compounds) are created in order to note how slight variations change biological activity. This type of process was key to the discovery in the '007 Patent and the '149 Patent as well as to Dr. Sutherland’s theory of obviousness.

B. *Earlier Discoveries*

[18] There is no serious issue about either the early discoveries; how the prior art came about or how the '149 Patent was developed. The sole issue is that the prior art made the '149 Patent obvious in that it was “obvious to try” to discover Ezetimibe.

[19] The Ezetimibe discovery came about as a result of a long process of research and study which began with the ACAT project in 1988. ACAT is an enzyme in the body which was thought to be involved in cholesterol trafficking – thus inhibiting it would presumably inhibit cholesterol absorption. The initial ACAT inhibitors synthesized were not beta-lactums or azetidinones. However, the team headed by Dr. Clader (a principal witness in this litigation and the inventor of the '007 and '149 Patents) moved to the beta-lactum structure.

[20] Initial in vivo and in vitro studies were unsatisfactory. The in vitro studies measured ACAT inhibition while in vivo studies measured cholesterol lowering activity in cholesterol fed hamsters. The problem with the studies was that the in vitro activity of some ACAT compounds bore no resemblance to the in vivo activity. The scientists therefore had no idea as to the mechanism of action.

[21] As a result, the Merck scientists abandoned in vitro studies, concentrated on in vivo and through extensive testing and trial and error, they discovered the compound SCH 4846 in October 1990.

[22] This was the basis for what is identified in the '007 Patent as Compound 9. The '007 Patent priority date was June 23, 1991.

[23] The '007 Patent is entitled *Substituted Beta-Lactum Compounds Useful as Hypocholesterolemic Agents and Processes for the Preparation Thereof*. It included a basic structure of beta-lactum compounds with substituents at the N1, C3 and C4 positions.

[24] A substituent is an atom or group of atoms substituted in place of a hydrogen on a parent atom. Ezetimibe is considered different from the compounds in the '007 Patent because of specific stereochemistry based on specific substituents and their placement.

[25] Because of the substituents at the three named positions, millions of compounds could be derived. In total, 228 compounds were tested in hamsters for cholesterol lowering activity. The patent includes both in vivo and in vitro data. It is this data which forms a critical basis of Dr. Sutherland's thesis that the '007 Patent made Ezetimibe obvious or obvious to try.

[26] By 1995, despite success in the clinical trials of SCH48461, the team led by Dr. Clader moved on and concentrated on finding what became Ezetimibe.

C. *'149 Patent*

[27] The project became the CAI Project (cholesterol absorption inhibition – assessing the effectiveness of the compounds in question). There were 40 full-time scientists engaged in the

project and it took three more years to discover Ezetimibe after synthesizing more than 1,000 compounds and conducting thousands of time consuming and difficult experiments.

[28] Merck's Dr. Clader outlined that since in vitro studies had been a problem, all work had to be done through in vivo studies – a more difficult form of SAR analysis given the large number of variables which could be reduced by in vitro studies.

[29] A critical problem, at least from Merck's perspective, was that they did not know the metabolic fate of the compounds. A graphic illustration of the problem of "the black box" was set out in Dr. Wentland's cross-examination:

[30] As part of the effort to determine the structure of Ezetimibe, Merck had to conduct a novel experiment examining the bile of rats which had been given SCH48461 "Bile Duct – Diverted Rat Model". The experiment involved taking bile from a donor rat, and dosing a recipient rat with that bile and cholesterol and then examining the deceased recipient rat. Having discovered activity in the bile, scientists found that the fraction with the most activity was comprised primarily of a metabolite, glucuronide. The metabolite had been compound 8F in the '007 Patent.

[31] The Merck scientists found that using 8F produced even greater activity when it was injected into the intestine of the recipient rat. This led to consideration of the CH substituent of this compound, which had previously been rejected from the '007 data because that data had indicated

lower activity. The Applicants argue that some of the '007 data led away from Ezetimibe; this is an example of the “teaching away” of the '007 Patent.

[32] Merck then determined that a C-4 phenol (formed by para-hydroxylation at the C4 phenyl ring) was desirable. Dr. Clader’s evidence was that his team was surprised that a metabolite could have such good activity, believing that the body generally makes foreign substances less active.

[33] Through further SAR work (some of the internal work is not publicly available), the team discovered:

(a) at the N1 para position a fluorine was necessary;

(b) at the C3 position, the hydroxyl group bonded (OH) and the side chain was 3 carbons in length with a phenol and a fluorine at the para position. This was a fact not evident to the Applicants from the work done on the '007 Patent.

[34] Significantly, the evidence is that a change in a single atom in the compound being studied would not result in Ezetimibe.

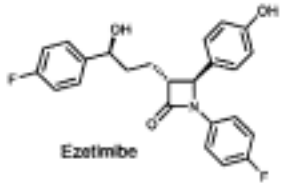
[35] Dr. Clader was not challenged by the Respondent on how difficult it was for Merck, and most particularly his team, to come upon Ezetimibe.

[36] It took almost two years from the filing date of the '007 Patent to the discovery of Ezetimibe (July 1992 – April 1994).

The '007 Patent was published in February 1993 and it was a further 16 months to June 1994 when the '149 Patent was filed. There is no evidence that explains why, despite allegedly being "obvious", no one else came up with Ezetimibe.

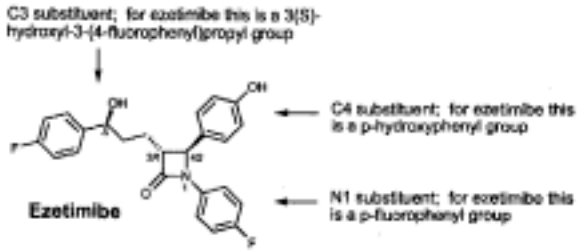
[37] Ezetimibe is a four-membered beta-lactum ring structure with certain specific constituents at the C4, C3 and N1 positions. Claim 21 of the '149 Patent describes Ezetimibe. It is the only claim at issue and there are no issues of claim construction.

Figure 2: Chemical drawing of ezetimibe from '149 Patent claim 21



[38] A more detailed drawing of Ezetimibe was contained in Dr. Wentland's affidavit.

Figure 1: Chemical drawing of ezetimibe depicting structural features



[39] The salient features of the above diagram and description of Ezetimibe is:

> The compound is trans (the C3 and C4 substituents point in opposite directions). The C3 substituent is "up" (3R) and the C4 substituent is

> "down" (4S), as is the benzylic hydroxyl substituent (S). It therefore has a fixed absolute stereochemistry of "3R, 4S".
>
> The substituents for the C3, C4 and N1 positions are as follows:
>
> - The C4 substituent is a para-substituted phenyl ring. The para-substitute is a hydroxyl group (called a "C4 phenol").
>
> - The C3 substituent is a hydroxyl-substituted carbon C3 side chain, specifically at the benzylic position. The C3 pendant phenyl ring of ezetimibe has a para-fluorine substituent.
>
> - Finally, there is also a para-flourine substitution on the N1 phenyl ring.

D. *POSITA*

[40] The parties are in agreement that the mythical "person of ordinary skill in the art" would be a person with an advanced degree in organic or medicinal chemistry and a few years' experience in conducting SAR analysis.

The advanced degree would be a Ph.D. or in the absence of that level of education, a MSc or BSc but with more years' experience.

[41] On a practical level, in oral argument, the parties acknowledged that the closest example to the POSITA would be a junior member of the Merck drug development team.

[42] One important area of disagreement is that Dr. Sutherland viewed familiarity with beta lactums as important, while Dr. Wentland disagreed on the basis that the bulk of experience with beta-lactums is in the context of anti-bacterials.

[43] It is evident in this case that skills related to drug development, SAR analysis and the treatment of drugs by the body – pharmacokinetics – are important areas of knowledge.

E. *Teva Evidence*

[44] The Respondents tendered one expert witness in Dr. John Sutherland, a professor at the University of Manchester. His background is in biological chemistry. Both before and after his Ph.D. at Oxford, he worked on beta-lactums as antibiotics. He teaches chemistry, biochemistry and the biology of drug actions.

[45] He has 60 peer reviewed articles, 18 related to beta-lactums but none in the field of hypocholesterolemics. In summary, his conclusions were:

- the '149 Patent was a non-inventive variant of compounds in the '007 Patent. The '149 Patent was obtained (and predicted to be obtained) through benzylic hydroxylation and substitution of a hydrogen atom for a fluorine atom at the para-position of phenyl groups.
- the '149 Patent merely claims an obvious metabolite of a previous compound without disclosing any unexpected advantages or non-obvious properties.
- as the compounds in the '007 Patent are extremely non-polar, they would be susceptible to oxidative metabolism.
- a POSITA would be knowledgeable about oxidative metabolic process and commonly used techniques in medicinal chemistry to increase and decrease

lipophilicity (attraction to fats) and increase or decrease the likelihood of oxidative metabolism.

[46] Therefore, in light of this knowledge, the '149 Patent was obvious because:

(a) the inventive concept is biological activity but the nature of the compounds and its activity were known.

(b) therefore, there is no inventive step and no experimentation or testing was necessary.

(c) the process of coming to Ezetimibe was like a 10 step additive sum – "anyone who can add can do it". The additive sum is based on trends in the '007 data which a POSITA could review using nothing more than a computer and would come to Ezetimibe.

[47] The 10 step additive sum in summary is:

1. the "backbone" of antihypercholesterolemic agents is disclosed.
2. the likelihood of oxidative metabolism is apparent because the compounds in the '007 Patent are non-polar and susceptible to oxidative metabolism. Sutherland relied heavily on a textbook by Burger (the Burger reference) to support these conclusions on drug biotransformations.
3. the '007 Patent disclosed optimal enantiomer.
4. the '007 Patent disclosed optimal absolute stereochemistry of the azetedinone/beta-lactum.

5. the '007 Patent disclosed optimal chain length of three carbons through a comparison of cis and trans series compounds.
6. the '007 Patent disclosed a requirement for a para-substituent at the C4 position.
7. the '007 Patent disclosed a requirement for C4 para-hydroxy substituent at the para-position.
8. the '007 Patent disclosed substitution of fluorine on the N-1 aryl group at the para-position.
9. the '007 Patent disclosed substitution of fluorine at the para-position of the C3 substituent.
10. a POSITA would have predicted the benzlic hydroxylation of the C3 carbon chain.

[48] It was acknowledged that one misstep within any of the 10 steps or a wrong conclusion on any of them would not produce Ezetimibe. There had to be perfection in each aspect of the additive sum.

[49] Dr. Sutherland's approach stands in marked contrast to the evidence of Merck's experts and to the actual steps taken to discover Ezetimibe.

F. *Merck's Evidence*

[50] The Court has already referred to the Applicants' evidence of how Ezetimibe was discovered. This evidence was principally from Dr. John Clader, a Ph.D. in organic chemistry and the lead inventor of the '007 and '149 Patents. It is obvious that he did not accept the notion that the

'149 Patent was obvious. His evidence detailed just how uncertain the process to discover Ezetimibe actually was.

[51] Dr. Mark Wentland is an expert in medicinal chemistry. He is a Professor (tenured) in the Department of Chemistry and Chemical Biology at Rensselaer Polytechnic Institute, Troy, NY. Dr. Wentland has taught undergraduate and graduate courses in medicinal chemistry, drug discovery and organic chemistry for 40 years. In addition, during the period 1970-1994, he was employed by the Sterling-Winthrop Research Institute (now part of Sanofi-Aventis) in the medicinal chemistry department.

[52] Dr. Wentland's research and medicinal chemistry teaching activities have focused on optimization, structure-activity relationships (SAR) and ADME characteristics of lead compounds with the ultimate goal of identifying a compound to enter clinical trials as a potential therapeutic to treat human disease. To this end, he made significant scientific contributions to the discovery and development of seven compounds that entered clinical trials (six from Sterling-Winthrop/Sanofi and one from Rensselaer). Since 1998, over 50 pharmaceutical and biotech companies worldwide have invited him to deliver a two-day workshop on various topics of medicinal chemistry, including lead optimization, SAR and ADME.

[53] His evidence was also a principal challenge to Dr. Sutherland's thesis. His expertise was in critical areas of SAR analysis and treatment of compounds in the body. He particularly points out the unique structure of Ezetimibe and concludes it would not be obvious. The substituents were not

contemplated in the '007 Patent and many of the tested compounds were shown to be less active than other alternatives. Many of the results in the '007 Patent taught away from Ezetimibe.

[54] Having taken issue with a number of Dr. Sutherland's steps, Dr. Wentland concluded that there was no reason to believe that the required combination of structural elements of Ezetimibe would lead to better activity than compounds in the '007 Patent. He emphasized that a single structural change could be significant and testing was required, a concept rejected by Dr. Sutherland.

[55] Dr. Neal Castagnoli is an expert in medicinal chemistry and drug metabolism. He is the Peters Professor of Chemistry (now Emeritus) at Virginia Polytechnic Institute and State University and has held that position since 1988. He received his Ph.D. in Chemistry from the University of California (Berkeley) in 1964 and entered academia in 1967. Since 1967, his teaching and research have been devoted primarily to medicinal chemistry and drug metabolism. In these areas of science he has over 250 articles published in revered research journals and has been a contributing author of over 50 review articles and books, many of which deal directly with oxidative metabolism of drugs and organic compounds, as well as metabolic bioactivation and detoxication of xenobiotics and Structure Activity Relationship (SAR).

[56] One of the books to which Dr. Castagnoli contributed as an author is Chapter 3 of *Burger's Medicinal Chemistry and Drug Discovery*. The fact of his authorship of Chapter 3 of *Burger's*, the chapter on metabolism, is significant because Dr. Sutherland relies on the book and the chapter as

one of the basis for his conclusion of the common knowledge of a POSITA. Yet, Dr. Castagnoli soundly rejects Dr. Sutherland's conclusions as to what a POSITA would know and how "obvious" the '149 Patent was alleged to be.

[57] Dr. Leslie Z. Benet is an expert in drug metabolism. He is a Professor and former Chairman of the Department of Biopharmaceutical Sciences at the University of California. He received his Ph.D. from the University of California in 1965. He was the founder of the *Journal of Pharmacokinetics and Biopharmaceutics* and has served (and currently serves) on the editorial boards of many scientific publications. He holds and has held elected positions with numerous scientific organizations and has served as a member of various U.S. government committees. Dr. Benet has received awards and distinctions from many scientific organizations. He has also received six honorary doctorates from universities in the United States and abroad. Dr. Benet is one of the most highly cited pharmacologists in the world having published almost 500 scientific articles and book chapters, all in the area of pharmcokinetics, biopharmaceutics, drug delivery and pharmacodynamics. Dr. Benet is internationally recognized as a leading expert on drug metabolism.

[58] His principal evidence is that there is considerable uncertainty in respect to the behaviour of metabolism and that even now testing is absolutely necessary. He notes that Dr. Sutherland ignored the possibility of Phase II metabolism and pointed out a number of inconsistencies in Dr. Sutherland's thesis.

[59] Dr. Antonio Gotto is an expert in cardiology and atherosclerosis. He is currently a Professor of Medicine, Provost for Medical Affairs at Cornell University and Dean of Weill Cornell Medical College. His qualifications in his field were similarly impressive to that of the other experts. His evidence related to the utility of Ezetimibe.

[60] Gary Thiessen, Vice President of Sales & Marketing for Primary Care at Schering-Plough Canada, gave evidence on the commercial success of Ezetimibe in Canada. His evidence addressed the commercial incentive of other pharmaceutical companies to discover Ezetimibe between the time of the publication of the '007 Patent and that of the '149 Patent.

G. *Differences between Prior Art and Ezetimibe*

[61] The prior art relied on in this case is the '007 Patent and most particularly the data which related to it showing the performance of various compounds.

[62] The difference between claim 21 of the '149 Patent and the '007 Patent is clearly set out in Dr. Wentland's evidence.

> The '149 Patent and, specifically claim 21, cover hypolipidemic compounds having unique structural features that are not contemplated in the billions of compounds covered by Formulas I and II of the '007 Patent. The differences between ezetimibe and what the skilled person would have understood from the '007 Patent in 1993 are that the specific C4 and C3 hydroxy-substituted substituents of ezetimibe claimed in claim 21 of the '149 Patent, when combined with the specific N1 substituent in a 3R,4S trans configuration, constitute a hypocholesterolemic compound falling outside the scope of Formulas I and II of the '007 Patent, which is far more active than the most potent compounds tested in the '007

> Patent. For the reasons described in my affidavit, none of these structural features would have been obvious to the skilled person.

[63] The Applicants' evidence is that there are at least four reasons why Ezetimibe would not be obvious:

1. The C4 substituent would not be obvious because the '007 Patent, particularly Compound 8F, had low activity (dealt with in the rat experiment; 8F taught away from OH; the data taught away from trans configuration). 8F as a solution was a "shot in the dark".
2. The N1 substituent (fluorine in the para position) would not be obvious because Compound 5D did not have good activity and its behaviour was uncertain.
3. The C3 substituent would not have been obvious because there was no data in the '007 Patent.
4. The activity of the new compound was not self-evident because a small structural change would have considerable effect. Ezetimibe is four structural changes away from the '007 Patent.

[64] The Applicants contend that there were too many unknowns to come to Ezetimibe easily. The discovery of Ezetimibe was more fraught with uncertainty than Dr. Sutherland's simple 10 step process would suggest. At the time the Applicants did not know what structure they were looking for.

III. ANALYSIS

A. *Issue*

[65] The sole issue in their litigation is whether the '149 Patent was obvious in light of the '007 Patent. The parties agree that this is a case engaging the “obvious to try” test. They disagree on the nature of that test and the application of it to the facts.

B. *Legal Test*

[66] The basic test for obviousness was set as “would a skilled but unimaginative workman have come directly and without difficulty to the solution taught by the Patent” (*Beloit Canada Ltd. v. Valmet OY*, [1986] F.C.J. No. 87, 8 C.P.R. (3d) 289).

[67] In *Beloit*, above, Justice Hugessen’s quote at page 294 sets the test at a high level:

> The test for obviousness is not to ask what competent inventors did or would have done to solve the problem. Inventors are by definition inventive. The classical touchstone for obviousness is the technician skilled in the art but having no scintilla of inventiveness or imagination; a paragon of deduction and dexterity, wholly devoid of intuition; a triumph of the left hemisphere over the right. The question to be asked is whether this mythical creature (the man in the Clapham omnibus of patent law) would, in the light of the state of the art and of common general knowledge as at the claimed date of invention, have come directly and without difficulty to the solution taught by the patent. It is a very difficult test to satisfy.

[68] The characterization of the POSITA was colourful and not meant to be a universal definition. It was used to underscore that the leap to obviousness had to be a short one. However,

there is a tension between a POSITA such as the one accepted here involving a Ph.D. and a few years of experience and the mythical creature who is somewhat close to a dunderhead.

[69] It must be remembered that the POSITA is a person of skill in the art so the degree of separation between the right and left hemisphere must reflect the characteristics of the notional POSITA. The person is neither first nor last in her class but somewhere in the middle.

[70] In this case, it is acknowledged that the POSITA is akin to a junior member of the drug development team. Would that person have come to Ezetimibe easily and directly? If so, why didn't she save Merck all the time, money and expense of the development team?

[71] For clarity those were rhetorical questions but they underline a critical flaw in the Respondent's case. There is no explanation offered either for the failure of that junior scientist to advise her superiors that there was an easier way (Dr. Sutherland's 10 steps) or given the expertise of the senior people on the team, why the junior scientist was not sent off to her computer to work through the data of the '007 Patent to discover Ezetimibe.

[72] The test for obviousness was recast by Justice Rothstein in *Apotex v. Sanofi Synthelabo Canada Inc.*, 2008 SCC 61. After a review of the relevant law and U.S. and U.K. law, Justice Rothstein recognized that *Beloit*, above, might be an overstatement of the law and that an "obvious to try" criterion should be incorporated into the obviousness test.

> **67** It will be useful in an obviousness inquiry to follow the four-step approach first outlined by Oliver L.J. in *Windsurfing*

> *International Inc. v. Tabur Marine (Great Britain) Ltd.*, [1985] R.P.C. 59 (C.A.). This approach should bring better structure to the obviousness inquiry and more objectivity and clarity to the analysis. The *Windsurfing* approach was recently updated by Jacob L.J. in *Pozzoli SPA v. BDMO SA*, [2007] F.S.R. 37 (p. 872), [2007] EWCA Civ 588, at para. 23:
>
> > In the result I would restate the *Windsurfing* questions thus:
> >
> > (1) (a) Identify the notional "person skilled in the art";
> >
> > (b) Identify the relevant common general knowledge of that person;
> >
> > (2) Identify the inventive concept of the claim in question or if that cannot readily be done, construe it;
> >
> > (3) Identify what, if any, differences exist between the matter cited as forming part of the "state of the art" and the inventive concept of the claim or the claim as construed;
> >
> > (4) Viewed without any knowledge of the alleged invention as claimed, do those differences constitute steps which would have been obvious to the person skilled in the art or do they require any degree of invention? [Emphasis added.]
>
> It will be at the fourth step of the *Windsurfing/Pozzoli* approach to obviousness that the issue of "obvious to try" will arise.

[73] While the obvious to try component arises at the 4th step, Justice Rothstein gives further guidance as to the operation of the test.

> **64** While I do not think the list is exhaustive, the factors set forth by Kitchin J. and adopted by Lord Hoffmann in *Lundbeck*, referred to at para. 59 of these reasons, are useful guides in deciding whether a particular step was "obvious to try". However, the "obvious to try" test must be approached cautiously. It is only one factor to assist in the obviousness inquiry. It is not a panacea for alleged infringers. The patent system is intended to provide an economic

encouragement for research and development. It is well known that this is particularly important in the field of pharmaceuticals and biotechnology.

65 In *Saint-Gobain PAM SA v. Fusion Provida Ltd.*, [2005] EWCA Civ 177 (BAILII), Jacob L.J. stated, at para. 35:

> Mere possible inclusion of something within a research programme on the basis you will find out more and something might turn up is not enough. If it were otherwise there would be few inventions that were patentable. The only research which would be worthwhile (because of the prospect of protection) would be into areas totally devoid of prospect. The "obvious to try" test really only works where it is more-or-less self-evident that what is being tested ought to work.

In *General Tire*, Sachs L.J. said, at p. 497:

> "Obvious" is, after all, a much-used word and it does not seem to us that there is any need to go beyond the primary dictionary meaning of "very plain".

In *Intellectual Property Law*, at p. 136, Professor Vaver also equates "obvious" to "very plain". I am of the opinion that the "obvious to try" test will work only where it is very plain or, to use the words of Jacob L.J., more or less self-evident that what is being tested ought to work.

66 For a finding that an invention was "obvious to try", there must be evidence to convince a judge on a balance of probabilities that it was more or less self-evident to try to obtain the invention. Mere possibility that something might turn up is not enough.

…

68 In areas of endeavour where advances are often won by experimentation, an "obvious to try" test might be appropriate. In such areas, there may be numerous interrelated variables with which to experiment. For example, some inventions in the pharmaceutical industry might warrant an "obvious [page294] to try" test since there may be many chemically similar structures that can elicit different biological responses and offer the potential for significant therapeutic advances.

> **69** If an "obvious to try" test is warranted, the following factors should be taken into consideration at the fourth step of the obviousness inquiry. As with anticipation, this list is not exhaustive. The factors will apply in accordance with the evidence in each case.
>
> > 1. Is it more or less self-evident that what is being tried ought to work? Are there a finite number of identified predictable solutions known to persons skilled in the art?
> >
> > 2. What is the extent, nature and amount of effort required to achieve the invention? Are routine trials carried out or is the experimentation prolonged and arduous, such that the trials would not be considered routine?
> >
> > 3. Is there a motive provided in the prior art to find the solution the patent addresses?
>
> **70** Another important factor may arise from considering the actual course of conduct which culminated in the making of the invention. It is true that obviousness is largely concerned with how a skilled worker would have acted in the light of the prior art. But this is no reason to exclude evidence of the history of the invention, particularly where the knowledge of those involved in finding the invention is no lower than what would be expected of the skilled person.

[74] *Sanofi*, above, confirmed that there was to be no inventive step but did recognize that some experimentation or routine testing could be involved but it could not constitute an undue burden.

[75] The “obvious to try” test was further refined in *Pfizer Canada Inc. v. Apotex Inc.*, 2009 FCA 8, by rejecting the “worth a try” test and to laying emphasis on “obvious” in the sense of “very plain”, “more or less self-evident”.

> **28** I take it from this that the test adopted by the Supreme Court is not the test loosely referred to as "worth a try". After having

> noted Apotex' argument that the "worth a try" test should be accepted (para. 55), Rothstein J. never again uses the expression "worth a try" and the error which he identifies in the matter before him is the failure to apply the "obvious to try" test (para. 82).
>
> **29** The test recognized is "obvious to try" where the word "obvious" means "very plain". According to this test, an invention is not made obvious because the prior art would have alerted the person skilled in the art to the possibility that something might be worth trying. The invention must be more or less self-evident. The issue which must be decided in this appeal is whether the Federal Court Judge failed to apply this test.

[76] Teva relies heavily on the U.K. decision of *Genetech Inc.'s Patent*, [1989] R.P.C. 147 (CA) at 276 where the U.K. Court of Appeal, considering an invention involving numerous steps, accepted that where a solution was found by pertinacity, sound technique or trial and error, the invention in question was obvious.

[77] However, when Justice Rothstein did his review of U.S. and U.K. law in the *Sanofi* decision, he did not mention, much less adopt, this U.K. law. Canada developed its own test and Teva's reliance on the *Genetech* decision is misplaced.

[78] The proper test is that set forth in *Apotex*, above, and as developed in *Pfizer*, above.

C. *Application of Canadian Test*

[79] Merck contends that Dr. Sutherland is unqualified to give evidence of what a POSITA would know and how she would be led to Ezetimibe. This is in part based on his field of expertise

and experience which is not directly related to anti-cholesterol beta lactums and his unfamiliarity with the common general knowledge of a POSITA.

[80] It is not so much that Dr. Sutherland is under qualified in this area (he may be over qualified in what a POSITA could do) but that the weight of his opinion is not as strong as that of Merck's experts, particularly Dr. Castagnoli.

[81] In trying to understand what a person of skill would know, Dr. Sutherland relied on *Burger's Medicinal Chemistry and Drug Discovery*, an acknowledged text forming part of the basis of common general knowledge. The very author of the text on metabolism in Chapter 3 on Drug Biotransformations, Dr. Castagnoli, disagrees that a person of skill would know the type of metabolite formed in the body.

[82] Dr. Castagnoli is in a better position to speak to the common general knowledge in the critical area of metabolism. He essentially "wrote the book" on the subject and he would likely know better than Dr. Sutherland what a person of skill would understand from the text. Therefore, the Court prefers Dr. Castagnoli's evidence.

[83] The issue of whether a POSITA would know what metabolites would form in the body and whether it was important, is critical to Dr. Sutherland's thesis. However, the weight of the evidence from experts with more direct experience and expertise than Dr. Sutherland is to the contrary of his

thesis. The Court accepts that contrary opinion evidence as being more reliable, less speculative and more soundly based.

[84] A further difficulty with Dr. Sutherland's opinion and particularly his 10 step process is that the process itself is subject to error, speculation and has traces of inventiveness in and of itself.

[85] In the 10 step process there are potentially too many mis-steps to qualify as something obvious, easy or self-evident. These are outlined in Merck's expert evidence.

(a) Step 1 (Backbone) involves thousands of compounds.

(b) Step 2 (Oxidation Metabilism) is inconsistent with Dr. Castagnoli's opinion. Actual metabolites cannot be predicted and it is uncommon that metabolites would show greater activity.

(c) Step 3 (Optimal Enantiomer) assumes that in stereochemistry trans are better than cis. However, two key compounds 8F and 1L show cis is better. Because the margin favouring trans is only 2:1, the margin is not great enough to exclude trying both.

(d) Step 4 (Absolute Stereochemistry) is dependent on an assumption by Dr. Sutherland which Dr. Wentland says should not be assumed but tested.

(e) Step 5 (Optimal Side Chain Length) is also based on assumptions which Dr. Wentland contends must be tested.

(f) Step 6 (Substituent of C4) is based on the use of two examples showing greater activity. However, there are nine other examples which show no improvement in activity at C4.

(g) Step 7 (OH at C4) is a particularly contentious area of debate. Merck's experts give nine reasons why this step is speculative and that the result could not be predicted.

(h) Step 8 (Fluorine at N1) is based on the conclusion that fluorine will block deleterious metabolism through lipophilicity. However, Dr. Sutherland admitted that other substances, e.g. iodine, give a greater desired effect. The evidence suggests that a POSITA would trend toward these other substances.

(i) Step 9 (Substitution of Fluorine at C3) suffers from the same criticism as Step 8.

(j) Step 10 (C3 Benzylic Hydroxylation) runs contrary to the knowledge a POSITA would have that flurone at C3 could prevent benzylic hydroxylation. As such, there is no way to predict behaviour.

[86] Aside from predictability, it was acknowledged that if there was one error in the 10 step process, one would not create Ezetimibe. An example of this risk of error is Dr. Sutherland's conclusion that one would know that a carbon only side chain was the obvious choice. Dr. Sutherland opined that it was known that an oxygen in the side chain was bad for activity. However, at pages 70 and 71 Vol. 1 of the Respondent's Record, is a table of compounds where several of the compounds have an oxygen in the side chain and yet have significant activity.

[87] On this evidence an oxygen would be an obvious choice, yet an oxygen in the side chain would never give up Ezetimibe.

[88] The Court cannot find that Dr. Sutherland's process was itself an obvious way to arrive at Ezetimibe. It may have been "worth a try" but that is not the applicable legal test. While potentially worth a try, it was not obvious to try. Indeed, Dr. Sutherland's 10 step process has all the earmarks of ingenuity and inventiveness. However, on a balance of probabilities, it was not more or less self-evident to obtain the invention in this way based on the prior art.

[89] There are other factors which make Dr. Sutherland's thesis of how the drug was obvious less convincing. In the 4th step of Justice Rothstein's analysis, factors such as testing, motive and actual course of conduct in obtaining the invention are to be considered.

[90] Dr. Sutherland's thesis is that one could arrive at Ezetimibe without ever testing the results of the various steps to achieve the result and without truly understanding what is actually happening. Given that what is being developed is a drug for human ingestion, this unfailing faith in the math is counter intuitive.

[91] It seems more likely that scientists engaged in this type of activity would or should want to know what is happening and why. This is what happened in reality in this case.

[92] The reality of how a drug was discovered is not always the complete answer to the claim of obviousness. There may be reasons which suggest that the patent, despite extensive development work, was obvious but none are advanced by the Respondent. There was no challenge to the efficiency, efficacy or motivation of Merck in the lead up to the discovery.

[93] The reality of Merck's efforts, the team working over an extended time, the time and money expended, the stops and starts, the successes and failures, the groping in the dark all belie Dr. Sutherland's approach that everything was there in front of Merck and all they had to do was perform the additive sum.

[94] To accept Teva's premise, the Court would have to conclude that Dr. Clader and his team "missed the boat" – that all their efforts were unnecessary.

[95] If the discovery was that simple, as Teva suggests, there is no evidence or explanation for the failure of other competitors to at least even begin down the path Dr. Sutherland outlined. There is a profit and competitive motive to develop a drug which now has established utility especially where to do so is as simple as the Respondents claim.

[96] In addition to the disparity between reality and thesis, there is no evidence that Dr. Sutherland's methodology has worked in the past. This may well be a situation where only someone of Dr. Sutherland's qualifications and experience could have created this approach but that suggests that the notional person of skill could not and did not.

[97] The Court cannot ignore that Dr. Sutherland knew what the result of his thesis should be. He knew the result and he then developed the methodology to achieve it. In a non-technical sense he reverse engineered the patent.

[98] This is not to suggest any lack of integrity or honesty in Dr. Sutherland's opinion or belief or his sincere effort to divorce himself from this post-discovery knowledge. However, it is a simple human fact that matters are always simpler in hindsight. However, when working with the prior art, Merck not only did not know the steps to take or course to develop, it was not even certain of the destination. Dr. Sutherland had the benefit of knowing the destination; the course is not as difficult to plot.

IV. CONCLUSION

[99] For all these reasons, the Court cannot conclude that the '149 Patent was obvious or even obvious to try by virtue of the prior art Patent '007.

[100] Therefore, the application for an order prohibiting the Minister of Health from issuing a Notice of Compliance to Teva Canada Limited for its generic version of the drug Ezetimibe will be granted with costs.

JUDGMENT

THIS COURT ORDERS AND ADJUDGES that the application for an order prohibiting the Minister of Health from issuing a Notice of Compliance to Teva Canada Limited for its generic version of the drug Ezetimibe is granted with costs.

"Michael L. Phelan"
Judge

FEDERAL COURT

SOLICITORS OF RECORD

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