Date: 20090323

Docket: T-1561-07

Citation: 2009 FC 301

Ottawa, Ontario, March 23, 2009

PRESENT: The Honourable Mr. Justice Hughes

BETWEEN:

ELI LILLY CANADA INC.

Applicant

and

NOVOPHARM LIMITED and THE MINISTER OF HEALTH

Respondents

and

ELI LILLY AND COMPANY

Respondent/Patentee

REASONS FOR JUDGMENT AND JUDGMENT

[1] This is a proceeding brought under the provisions of the *Patented Medicines (Notice of Compliance) Regulations*, SOR/93-133, as amended (*NOC Regulations*). The Applicant is seeking to prohibit the Minister of Health from issuing a Notice of Compliance to the Respondent Novopharm Limited for a generic version of the Applicant's raloxifene hydrochloride medicine until the expiry of Canadian Letters Patent No. 2,158,399 (the '399 patent).

[2] In a related proceeding heard at the same time (T-1562-07) the Applicant is seeking to prohibit the Minister from issuing a Notice of Compliance to Novopharm Limited in respect of its generic version of the same drug until the expiry of Canadian Patent 2,250,191 (the ’191 patent).

[3] A third proceeding between these parties respecting the same medicine, Court file No. T-1563-07 has been adjourned *sine die* by an Order of Prothonotary Tabib dated January 6, 2009 and is not of any relevance to this present proceeding. I am informed that this proceeding relates to Canadian Patent No. 2,101,356 which was the subject of my decision cited as 2008 FC 142 and is currently under appeal.

[4] For the reasons that follow, I find that the application is dismissed with costs payable by the Applicant to Novopharm.

THE PARTIES

[5] The Applicant Eli Lilly Canada Inc. (Lilly Canada) has received from the Minister of Health (Minister) a Notice of Compliance respecting a medicine containing raloxifene hydrochloride in 60 mg tablet form which medicine the Applicant markets in Canada under the brand name EVISTA under Drug Identification Number (DIN) 02239028. This medicine is used in the treatment and prevention of osteoporosis. This party is referred to as the “first person” under the *NOC Regulations*.

[6] The Respondent Novopharm Limited (Novopharm) sent a Notice of Allegation to Lilly Canada stating that it intends to market a generic version of such 60 mg tablets containing raloxifene hydrochloride and is seeking to obtain a Notice of Compliance from the Minister to do so by filing an Abbreviated New Drug Submission (ANDS) in which Lilly Canada's product has been referenced. This party is referred to as the "second person" under the *NOC Regulations*.

[7] The Respondent Minister is charged with administering the *NOC Regulations* and issuing a Notice of Compliance where appropriate.

[8] The Respondent Eli Lilly and Company (Lilly US) is the patentee of the '399 patent and has been made a party to these proceedings in accordance with section 6(4) of the *NOC Regulations*.

THE PATENT AT ISSUE

[9] At issue is Canadian Letters Patent No. 2,158,399 (the '399 patent). The application for that patent was filed with the Canadian Patent Office on September 15, 1995, thus, the patent is governed by the provisions of the *Patent Act*, R.S.C. 1985, c. P-4, as they stand following amendments made October 1, 1989. These provisions may be referred to as the new *Patent Act*.

[10] The application for the '399 patent was laid open for public inspection on March 20, 1996. This becomes an important date in construing the patent. The application for the patent claims priority from applications filed in the United States Patent Office on September 19, 1994 and April 26, 1995. The '399 patent will expire 20 years from the date of filing the application in Canada, that

is, on September 15, 2015. The ’399 patent was issued and granted on March 20, 2001. That date is not particularly important in these proceedings save to indicate that the patent has been issued and granted.

[11] At page 1 the patent states in the opening paragraph that it is directed to what is described as a novel, non-solvated crystalline form of a class of chemicals described by a written formula:

> *This invention is directed to a novel pharmaceutical product. More particularly, the invention is directed to a novel, non-solvated, crystalline form of a 2-aryl-6-hydroxy-3-[4-(2-aminoethoxy) benzoyl] benzo[b]thiophene.*

[12] In particular the patent deals with a particular member of that class identified by the formula set out in the second paragraph of page 1:

> *6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl] benzo[b]-thiophene hydrochloride*

[13] Fortunately, the patent at the same page, as well as the parties, have used the name raloxifene hydrochloride or raloxifene HCl in place of the written formula. I will also do so.

THE EVIDENCE

[14] The evidence in this proceeding was provided, as is usual in applications before this Court, by way of affidavits, exhibits to affidavits, transcripts of cross-examination and exhibits to those cross-examinations. A Protective Order was granted in this proceeding on October 15, 2007 however, given that the issues are reduced from those set out in the Notice of Allegation, only the

issue of validity is now before the Court thus no part of the evidence as to that issue remains confidential.

[15] The Applicant filed affidavits from the following witnesses :

- Dr. Joel Bernstein, a full professor of chemistry at Ben-Gurion University of Negev, Beer Sheva, Israel. He claims expertise in the areas of polymorphism, crystallography and organic solid state chemistry.
- Nancy Gallagher, a law clerk employed by the Applicant's law firm. She provided copies of the Notice of Allegation, the patent at issue, certain prior art references and the Notice of Application. None of these documents are contested.
- Dr. Leonard J. Chyall, a research investigator, currently a principal in the consulting division of Aptuit, an independent research laboratory. He attempted to reproduce Examples 16 and 18 of United States Patent No. 4,418,068 (the '068 patent) and reviewed the work of Dr. Ferrari, one of Novopharm's witnesses. This affidavit was filed in reply.

[16] Drs. Bernstein and Chyall were cross-examined. Their claim to be experts was not contested; however Novopharm took issue with the claimed area of expertise of Dr. Bernstein.

[17] The Respondent Novopharm filed affidavits from the following witnesses:

- Dr. Massimo Ferrari, director of Research and Development at Erregierre S.P.A. an Italian pharmaceutical manufacturer. He presented evidence as to his synthesis of a chemical compound said to be in accordance with Examples 16 and 18 of the ’068 patent. This evidence, according to Novopharm’s Counsel’s submission at the hearing, was presented as factual evidence. Dr. Ferrari also presented evidence in sur-reply to Dr. Chyall which was submitted as expert evidence. His sur-reply affidavit also contained evidence as to further experiments conducted by Dr. Ferrari which evidence was struck out by an Order of the Prothonotary. However remaining in evidence is some discussion as to those experiments by Dr. Chyall and Dr. Stradi in their cross-examinations.
- Dr. (Professor) Riccardo Stradi, a professor in the Department of Organic Chemistry, Faculty of Pharmacy at the University of Milan, Italy. He conducted X-Ray Powder Diffraction (XRPD) analysis on samples of material produced by Dr. Ferrari. This evidence was tendered as expert evidence.
- Dr. (Professor) Thomas T. Tidwell, a professor emeritus at the University of Toronto, Department of Chemistry. He claimed expertise in the area of synthesis, purification analysis and structural indentification of organic compounds. He reviewed the patent at issue, the prior art including the ’068 patent and a Jones article and the evidence of Dr. Bernstein.
- A. Louise McLean, a law clerk in Novopharm’s law firm’s offices. She provided copies of the Notice of Allegation and the prior art referred to therein. This evidence is not contested.

[18] Each of Drs. Ferrari, Stradi and Tidwell were cross-examined.

[19] The Minister did not file any evidence nor participate actively in this proceeding. Lilly US did not participate actively in this proceeding. I assume that its interests were looked after by Lilly Canada.

[20] I endorse the sentiments expressed by Harrington J. of this Court in *Lundbeck Canada Inc. v. Canada (Minister of Health),* 2009 FC 146 at paragraph 74 where he wrote that we really do not have evidence by way of actual persons or even "talking heads" in proceedings such as this, we simply have words on pieces of paper. Other than in the most exceptional cases, a Court is not in a position to come to any conclusions as to whether certain witnesses were evasive, or acted as advocates or acted in other ways urged by counsel so as to encourage the Court to take a dim view as to demeanour of any other party's witnesses. I add my voice to those crying in the wilderness for improvements in the process.

MOTION TO STRIKE

[21] At the outset of the hearing Lilly Canada brought a motion requesting that the Court strike out the first affidavit of Dr. Massimo Ferrari, the sur-reply affidavit of Dr. Ferrari including Exhibits A and B, and the affidavit of Mr. Riccardo Stradi including Exhibits A, B, C and D, all of which had been submitted by Novopharm together with the transcripts of the cross-examinations of Drs.Ferrari and Stradi and, as Applicant's counsel agreed at the hearing, also including the Applicant's own

evidence comprising the affidavit of Dr. Chyall and the transcript of his cross-examination. I did not grant the motion, all this evidence shall remain in the Record, subject to weight.

[22] The basis for the motion was twofold:

a. The cross-examination of Dr. Ferrari showed that Novopharm and a related company Teva, were clients of the company that he works for, Erregierre, thus, it was argued, he was likely to be biased; and

b. The experiments performed by Dr. Ferrari were irrelevant and in any event the results were questionable.

[23] I rejected both grounds of argument. First, as to the allegation of bias. This allegation is based on answers to two questions put to Dr. Ferrari on cross-examination as follows:

> *Q. The company that you work for, Erregierre, they are the supplier of Novopharm in Canada, is that correct?*
>
> *A. I do not deal with the commercial activity of the company and therefore I cannot give you a definite answer. But as far as I know, Novopharm is one of our clients.*
>
> *Q. And Teva as well?*
>
> *A. Yes.*

[24] This exchange cannot be said to give rise to any question of bias sufficient to exclude Dr. Ferrari's evidence. At best it shows that he works for a company that has, among its clients, Novopharm and Teva. We don't know if the product at issue is involved, whether the clients are major or trivial, nor whether the clients were in any position to exert influence over Dr. Ferrari or

the experiments performed by him. The Court will exercise caution in looking at Dr. Ferrari's evidence, but, without more, that caution would be the same as looking at the evidence of any outside expert that the Court knows full well is being compensated by the party tendering his or her evidence.

[25] Secondly as to the soundness of the evidence, that is a matter to be considered in the context of all the evidence in the proceeding. I was not persuaded that the experiments conducted were so unsound as to be removed from the Record. The evidence shall remain, subject to weight.

ISSUES

[26] The issues in this proceeding relate to validity of the claims of the '399 patent having regard to:

a. Anticipation

b. Obviousness

The Respondent Novopharm had also raised a mixed question of validity and infringement on the basis of what is known as the Gillette Defence. At the outset of the hearing Novopharm's Counsel advised that this matter was withdrawn.

BURDEN OF PROOF

[27] The issue as to who bears the burden of proof in NOC proceedings, as to validity of a patent or infringement of a patent, is an issue that I had thought had been put to rest. Nonetheless the parties in such proceedings continue to argue the point. It seems that my recent decision in *Brystol-*

Myers Squibb Canada Co. v. Apotex Inc., 2009 FC 137 has given fresh ammunition to those continually wishing to stir the pot in this regard. Let me state emphatically that I did not intend in *Brystol-Myers* to say or apply any burden different than I had stated in previous decisions.

[28] To be perfectly clear, when it comes to the burden as to invalidity I canvassed the law, in particular recent Federal Court of Appeal decisions, in *Pfizer Canada Inc. v. Canada (Minister of Health)*, (20008), 69 C.P.R. (4th) 191, 2008 FC 11 and concluded at paragraph 32:

> ***32*** *I do not view the reasoning of the two panels of the Federal Court of Appeal to be in substantial disagreement. Justice Mosley of this Court reconciled these decisions in his Reasons in Pfizer Canada Inc. v. Apotex Inc., [2007] F.C.J. No. 1271, 2007 FC 971 at paragraphs 44 to 51. What is required, when issues of validity of a patent are raised:*
>
> > *1. The second person, in its Notice of Allegation may raise one or more grounds for alleging invalidity;*
> > *2. The first person may in its Notice of Application filed with the Court join issue on any one or more of those grounds;*
> >
> > *3. The second person may lead evidence in the Court proceeding to support the grounds upon which issue has been joined;*
> >
> > *4. The first person may, at its peril, rely simply upon the presumption of validity afforded by the Patent Act or, more prudently, adduce its own evidence as to the grounds of invalidity put in issue.*
> >
> > *5. The Court will weigh the evidence; if the first person relies only on the presumption, the Court will nonetheless weigh the strength of the evidence led by the second person. If that evidence is weak or irrelevant the presumption will prevail. If both parties lead evidence, the Court will weigh all the*

> *evidence and determine the matter on the usual civil balance.*
>
> *6. If the evidence weighed in step 5 is evenly balanced (a rare event), the Applicant (first person) will have failed to prove that the allegation of invalidity is not justified and will not be entitled to the Order of prohibition that it seeks.*

[29] I stated the matter more succinctly in *Pfizer Canada Inc. v. Canada (Minister of Health)*, 2008 FC 500 at paragraph 12:

> ***12*** *Here the only issue is validity. Pharmascience has raised three arguments in that respect. Each of Pfizer and Pharmascience have led evidence and made submissions as to those matters. At the end of the day, I must decide the matter on the balance of probabilities on the evidence that I have and the law as it presently stands. If, on the evidence, I find that the matter is evenly balanced, I must conclude that Pfizer has not demonstrated that Pharmascience's allegation is not justified.*

[30] The above cases state correctly, in my view, the law as to the burden in NOC proceedings as to invalidity.

[31] Turning to infringement the law is well settled that where a generic has alleged non-infringement, the statements that it makes in that regard in its Notice of Allegation are presumed to be true. The Applicant (first party) bears the burden of proof, on the balance of probabilities, to satisfy the Court that the allegations of non-infringement are not justified; merely to raise the possibility of infringement is insufficient. The Federal Court of Appeal made these points quite

clearly in its decision in *Novopharm Limited v. Pfizer Canada Inc.* (2005), 42 C.P.R. (4th) 97, 2005 FCA 270 at paragraphs 19, 20 and 24:

> ***19*** *In Pharmacia Inc. v. Canada (Minister of National Health and Welfare) (1995), 64 C.P.R. (3d) 450 (F.C.A.), Hugessen J.A. addressed the evidentiary burden placed on a generic under the Regulations. He adopted the reasons of the trial judge who described this burden as follows:*
>
> > *... the grounds that the patentee has for challenging the generic's notice of allegation should be advanced in the originating notice of motion filed pursuant to s. 6(1) of the Regulations. ... The generic may then be informed as to what vexes the patentee and why a prohibition order barring entry should be issued. Initially, i.e., before the Minister, the generic has raised the issue of non-infringement. At this stage, before the court, the generic now has the opportunity to file evidence supporting its detailed statement. In essence, this is the evidential burden on a respondent.*
> >
> > *(see Pharmacia Inc. v. Canada (Minister of National Health and Welfare) (1995), 60 C.P.R. (3d) 328 at 339-40 (F.C.T.D.), per Wetston J.)*
>
> ***20*** *In my view, this statement remains good law. Where, as here, the NOA is found to be adequate, the legal burden remains squarely on Pfizer to prove, on a balance of probabilities, that the allegations in the NOA are unjustified. Novopharm has no evidential burden to support the allegations in its NOA and detailed statement (see AB Hassle 2 at paragraph 35). Therefore, Novopharm need only file evidence supporting its detailed statement to counter evidence, if any, submitted by Pfizer in the course of the prohibition proceedings.*
>
> …
>
> ***24*** *For whatever reason, Pfizer relies solely on Dr. Munson's speculations in this proceeding. The law is well settled that in order to satisfy the legal burden placed on it under section 6 proceedings, it is insufficient for Pfizer to merely raise the possibility of infringement (see Glaxo Group Ltd. v. Canada*

> *(Minister of National Health and Welfare) (1998), 80 C.P.R. (3d) 424 (F.C.T.D.) at paragraph 9). In relying solely on Dr. Munson's evidence, Pfizer has failed to satisfy its legal burden of proving that Novopharm's NOA is not justified.*

CONSTRUCTION OF THE PATENT-GENERALLY

[32] Before embarking upon a consideration as to validity of the patent, the Court is required to construe the patent and its claims. Construction of this patent, which is a "new" *Patent Act* patent, is done as of the date of its publication, March 20, 1996 through the eyes of a person skilled in the art, taking into consideration the knowledge that such a person would possess as of that date. Construction must take into consideration the whole of the patent, its disclosure and claims. Expert assistance, where needed, may be provided to provide the meaning of certain terms and the knowledge that a person skilled in the art would have had as of that date. As Sharlow JA. for the Federal Court of Appeal panel said in *Novopharm Limited v. Janssen-Ortho Inc.* (2007), 59 C.P.R. (4th) 116, 2007 FCA 217 wrote at paragraph 4:

> *Construction of Claim 4*
> ***4*** *In any case in which the validity or infringement of a patent claim is in issue, it is necessary to construe the claim: Whirlpool Corp. v. Camco Inc., [2000] 2 S.C.R. 1067 at paragraph 43. The relevant date for the construction of the 080 patent is the date of its issuance, June 23, 1992. The patent must be understood as being addressed to a person skilled in the art, taking into consideration the knowledge that such a person is expected to possess on that date. The construction of a patent claim is a task for the Court and must be based on the whole of the disclosure and the claim, assisted by expert evidence as to the meaning of certain terms and the knowledge that a person skilled in the art is expected to possess on the relevant date.*

[33] She was speaking of an "old" *Patent Act* patent which is to be construed as of the date of its grant but otherwise her words are equally appropriate to a "new" *Patent Act* patent.

PERSON SKILLED IN THE ART

[34] The parties did not devote any significant attention either in written or oral argument to defining the notional person or persons skilled in the art to whom the patent is said to be directed.

[35] Assistance can be de derived from the first page of the ’399 patent itself which states that the invention is directed to a novel pharmaceutical product namely a non-solvated crystal of a compound known as raloxifene which is produced by the use of a hitherto unknown synthetic process. It says:

> *This invention is directed to a novel pharmaceutical product. More particularly, the invention is directed to a novel, non-solvated, crystalline form of a 2-aryl-6-hydroxy-3-[4-(2-aminoethoxy) benzoyl] benzo[b]thiophene.*
>
> …
>
> *In accordance with the present invention, the Applicants have now discovered that a novel, non-solvated crystalline form of raloxifene can be produced, free of, for example, chlorobenzene and aluminium contaminants, by the use of a hitherto unknown synthetic process.*

[36] Thus one would expect that a person skilled in the art would be familiar with crystalline forms of pharmaceutical products such as raloxifene and known processes as to how they might be produced.

[37] The Applicant’s expert, Dr. Bernstein defined a person skilled in the art in paragraph 27 of his Affidavit as follows:

> *As the subject matter of the claims in question relates to a new crystal form of raloxifene hydrochloride, I would consider a person skilled in the art to be a person with at least a Bachelor of Science in*

> *chemistry and at least a couple years experience working or conducting research in the drug development process with some exposure to polymorphic compounds and their characterization.*

[38] Novopharm's expert, Dr. Tidwell described a person skilled in the art in paragraph 11 of his Affidavit:

> *11. In my opinion, the 399 Patent is directed to a person with a degree in organic chemistry and a minimum of several years experience in the synthesis of organic chemical compounds, including drug molecules. This person would be familiar with, and experience in, the area of synthesis, crystallization and purification of drug molecules and would understand the role of XRPD in distinguishing crystalline structures from one another. I will refer to such a person as the "person skilled in the art".*

[39] There is little difference between the two experts except that Dr. Tidwell also states that the person skilled in the art should have some reasonable knowledge as to synthesis of organic compounds. I agree. It must be recognized that the person skilled in the art, must know not only about crystal forms but also how to produce them.

CONSTRUCTION OF THE '399 PATENT-SPECIFICALLY

[40] The introductory paragraph of the '399 patent at page 1 states that the invention is directed to what it describes as a novel pharmaceutical product, a non-solvated, crystalline form of raloxifene:

> *This invention is directed to a novel pharmaceutical product. More particularly, the invention is directed to a novel, non-solvated, crystalline form of a 2-aryl-6-hydroxy-3[4-(2-aminoethoxy) benzoyl] benzo[b]thiophene.*

[41] Following this paragraph, at page 1 of the ’399 patent is an acknowledgement that raloxifene hydrochloride is a previously known pharmaceutical agent. Reference is made to U.S. Patent No. 4,418,068 (the ’068 patent) and what has become known in these proceedings as the “Jones Article” in this regard. The ’068 patent and Jones Article are important in discussing the validity questions. The ’399 patent states that the compound is difficult to purify, it contains solvent and other contamination and has an unpleasant odor:

> *U.S. Patent No. 4,418,068 describes 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl] benzo[b]-thiophene hydrochloride, known as raloxifene hydrochloride, which has shown particular promise as a pharmaceutically-active agent. Unfortunately, this compound has proven extremely difficult to purify. Particular problems have arisen due to solvent contamination. For instance, the process described in the Journal of Medicinal Chemistry, 27(8), 1057-1066 (1984), for synthesizing raloxifene suffered from the serious shortcoming that it produced a solvated compound contaminated with chlorobenzene, a known cancinogen. Further, other processes described in the literature utilized a classical aluminum chloride-catalyzed Friedel-Crafts acylation. The product of these processes contain aluminum contaminants and various thioester by-products, which are difficult to remove. Also the product of these literature processes has an unpleasant residual thiol or sulphide odor.*

[42] Next, and still at page 1, the “discovery” made by the named inventors is concisely described: it is that a novel, non-solvated crystalline form of raloxifene can be produced free of certain contaminants, by what is described as a hitherto unknown process:

> *In accordance with the present invention, the Applicants have now discovered that a novel, non-solvated crystalline form of raloxifene can be produced, free of, for example, chlorobenzene and aluminum contaminants, by the use of a hitherto unknown synthetic process.*

[43] The "new process" is described at pages 6 and 7 of the patent in saying that "…*(t)he new process eliminates the use of aluminum and the odorous mercaptans and sulfides*".

[44] The novel crystal form of the alleged invention is identified beginning at the bottom of page 1 of the '399 patent over the middle of page 3, by two columns of numbers produced by the X-Ray diffraction (XRPD) technique (Table 1). The experts are agreed that such numbers called a "pattern" represent a "fingerprint" which is unique to this particular crystal form of raloxifene hydrochloride. For instance another crystal form of that compound will have a different "fingerprint" or "pattern". I will not reproduce the column of numbers here.

[45] What is important to note is that the patent does not ascribe any particular reason why the so-called novel crystal form is any better than any other form, no particular advantage as to the form is described no unique feature is given. It seems just to have that form and nothing more.

[46] At pages 3 and 4 of the patent, the reader is told that this new form should be at least 95% raloxifene hydrochloride, preferably 98% or 99%, and "substantially free" from chlorobenzene, aluminium salts and organoaluminum impurities, and substantially odor free. Each of these characteristics are defined as to what constitutes "substantially free" in respect of each unwanted impurity. It says:

> *Preferably, in the new, non-solvated form of raloxifene hydrochloride, the amount of 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl] benzo[b]-thiophene hydrochloride present in the crystalline material is at least 95% by weight (w/w), preferably at least 98%, more preferably at least 99%. More particularly, this preferred form is substantially free from*

> *chlorobenzene. Further, this preferred form is also substantially free from aluminum salts or organoaluminum impurities. Also, this preferred form is substantially odor free.*
>
> *The term "substantially free from chlorobenzene", as used herein in reference to the non-solvated crystalline 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl] benzo[b]-thiophene hydrochloride, represents a compound containing less than 5% of chlorobenzene calculated on a weight basis (w/w). Preferably, the amount of chlorobenzene is less than 2%, more preferably less than 1%. Most preferably, the amount of chlorobenzene in the non-solvated crystalline material is less than 0.6%.*
>
> *The term "substantially free from aluminum salts or organoaluminum impurities", as used herein in reference to the non-solvated crystalline describes 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl] benzo[b]-thiophene hydrochloride, represents a crystalline compound containing less than 5% of aluminum salts or organoaluminum impurities calculated on a weight basis (w/w). Representative aluminum salts include, but are not limited to, aluminum hydroxide, aluminum oxides, and hydrated forms thereof. Representative organoaluminum impurities include, but are not limited to, aluminum alkoxides, aluminum(III) complexed to the formula I or IV compounds, and thioaluminates. Preferably, the amount of aluminum salts or organoaluminum impurities is less than 2%, more preferably less than 1%.*
>
> *The term "substantially odor free", as used herein in reference to the non-solvated crystalline 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl] benzo[b]-thiophene hydrochloride, represents a compound containing less than 3% of mercaptan or sulfide impurities. Preferably, the amount of mercaptan or sulfide impurities is less than 2%, more preferably less than 1%. Representative mercaptan or sulfide impurities include, but are not limited to, C_1-C_6 alkylthiols and methyl C_1-C_6 alkyl sulfides.*

[47] The resulting product, the patent says at page 4 is more pure than the material produced by previous processes described in the literature and that it is free of aluminum and chlorinated

aliphatic solvents and aromatic solvents and therefore is preferred for use in making pharmaceutical compositions:

> *The non-solvated crystalline material is more pure than the material produced by the processes described in the literature. The present material is free from aluminum impurities, as well as, chlorinated aliphatic hydrocarbon solvents and aromatic solvents. The non-solvated crystalline form is particularly preferred for use in the manufacture of pharmaceutical compositions.*

[48] The statement that the product is free of aluminum and chlorinated aliphatic hydrocarbon solvents and aromatic solvents is at odds with the statements at pages 3 and 4 of the patent to the effect that the product is only "*substantially free*" of such impurities, with less than 2% and preferably less than 1% of such impurities. It is as if someone at a later time in drafting the patent had decided to hedge their bets. The new process is said not to use aluminum or the aromatic solvents at all. Why they should be said to appear in the final product is a question that the patent does not answer.

[49] Beginning at the bottom of page 4 of the '399 patent to the end of the description at page 25 is a description of the process to make this purer form of the product and several Examples in that regard are given. It is important to note that at pages 15 and 16 there is provided Table 2 which are two columns of numbers comprising an X-ray Diffraction "pattern" for a crystal form of raloxifene hydrochloride which is different from that shown in Table 1 at pages 2 and 3 of the patent. This different form is called Form I at page 15 but the parties are agreed that this is a misnomer and should be Form II. In the Examples provided Example 2, 3 and 6 are said to be directed to Form I (Table 1) and Example 4 is said to be directed to Form II (Table 2). The parties are agreed however

that Example 3 is really directed to Form II (Table 2) and that the reference is that Example to Form I is incorrect.

[50] In the claims, only Form I (Table 1) is claimed. The claims are directed only to "non-solvated" crystalline raloxifene hydrochloride. Any other form mentioned in the description of the patent, such as Form II is solvated. Solvated means that a measured quantity of the solvent used in the process from which the crystal is produced remains bound within the molecular lattice structure of the crystal itself.

THE CLAIMS OF THE '399 PATENT

[51] The '399 patent contains 8 claims. Claims 1 to 5 are directed to Form I non-solvated crystalline raloxifene hydrochloride. Claim 6 is directed to a pharmaceutical formulation containing such material. Claim 7 is directed to use of such material as a pharmaceutical.

[52] The claims (omitting the page and a half of X-Ray pattern data) are:

> *1. Non-solvated crystalline 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl] benzo[b]-thiophene hydrochloride exhibiting substantially the following X-ray diffraction pattern obtained with copper radiation:*
>
> *[Table 1]*
>
> …
>
> *2. The crystalline 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl] benzo[b]-thiophene hydrochloride of Claim 1 wherein the amount of 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl] benzo[b]-thiophene hydrochloride present is at least 95% by weight.*
>
> *3. The crystalline 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl] benzo[b]-thiophene hydrochloride of any*

> *one of Claims 1 and 2 which is substantially free from chlorobenzene.*
>
> *4. The crystalline 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl] benzo[b]-thiophene hydrochloride of any one of Claims 1, 2 and 3 which is substantially free from aluminum salts or organoaluminum impurities.*
>
> *5. The crystalline 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl] benzo[b]-thiophene hydrochloride of any one of claims 1-4 which is substantially odor free.*
>
> *6. A pharmaceutical formulation comprising the crystalline compound as claimed in any one of Claims 1 to 5 and one or more pharmaceutically-acceptable carriers, diluents, or excipients.*
>
> *7. The crystalline compound as claimed in any one of Claims 1 to 5 for use as a pharmaceutical.*

[53] The chemical formula can be replaced with the words raloxifene hydrochloride such that the claims read:

> *1. Non-solvated crystalline raloxifene hydrochloride exhibiting substantially the following X-ray diffraction patterns obtained with copper radiation:*
>
> *[Table 1]*
>
> *2. The crystalline raloxifene hydrochloride of claim 1 wherein the amount of raloxifene hydrochloride present is at leaset 95% by weight.*
>
> *3. The crystalline raloxifene hydrochloride of any one of Claims 1 and 2 which is substantially free from chlorobenzene.*
> *4. The crystalline raloxifene hydrochloride of any one of Claims 1, 2 and 3 which is substantially free from aluminum salts or organoaluminum impurities.*
>
> *5. The crystalline raloxifene hydrochloride of any of claims 1-4 which is substantially odor free.*

> *6. A pharmaceutical formulation comprising the crystalline compound in any one of Claims 1 to 5 and one or more pharmaceutically acceptable carriers, diluents, or excipients.*
>
> *7. The crystalline compound in any of claims 1 to 5 for use as a pharmaceutical.*

[54] The Court must construe these claims having in mind what a person skilled in the art would understand them to mean and having regard to the disclosure. As to the disclosure I have particular regard to those portions set out earlier in these reasons as to what is meant by "substantially free" of various substances and odors.

[55] While I am not bound by their construction, I also have had regard to the meaning given to these claims by the Applicant's expert Dr. Bernstein at paragraphs 28 to 37 of his affidavit and Novopharm's expert Dr. Tidwell at paragraphs 45 to 52 of his affidavit.

[56] I find, as a matter of construction of the claims of the '399 patent, that the essential elements of each claim are:

- Claim 1: a form of raloxifene hydrochloride having the following characteristics:
    - it is crystalline
    - it is non-solvated
    - it exhibits the particular x-ray diffraction pattern as set out in Table 1

  It need not be pure.

- Claim 2: The form of raloxifene hydrochloride of claim 1 that is at least 95% pure.
- Claim 3: The form of raloxifene hydrochloride of claims 1 or 2 which contains less than 5% by weight of chlorobenzene.
- Claim 4: The form of raloxifene hydrochloride of claims 1, 2 or 3 which contains less than 5% by weight of aluminium salts or organoaluminium impurities.
- Claim 5: The form of raloxifene hydrochloride of claims 1, 2, 3 or 4 which is substantially odor free in that it contain less than 3% by weight or mercaptan or sulphide impurities.
- Claim 6: A pharmaceutical formulation containing the form of raloxifene hydrochloride of any of claim 1 through 5.
- Claim 7: The form of raloxifene hydrochloride of any of claims 1 through 5 used as a pharmaceutical composition.

[57] Nowhere in the ’399 patent or in the evidence has there been shown to exist any form of raloxifene hydrochloride that is both crystalline and non-solvated that has an x-ray diffraction pattern other than Table 1. There are solvated crystalline forms having other patterns, but no non-solvated form has been shown to exist that has an x-ray diffraction pattern other than that of Table 1. The experts have said either in their affidavits or in cross-examination that there is a theoretical possibility that a form that is crystalline and non-solvated having a different x-ray diffraction pattern may in the future be found or created. The fact remains that at present the only known form of

raloxifene hydrochloride that is both crystalline and non-solvated is that having the pattern or "fingerprint" of Table 1.

PRIOR ART

[58] The challenges to validity of the '399 patent are two fold, anticipation and obviousness. As stated in many decision of the Courts such as the Federal Court of Appeal in *Imperial Tobacco Ltd. v. Rothmans Benson & Hedges Inc.* (1993), 47 C.P.R. (3d) 188 per Desjardins JA. at pages 197 to 199, as well as the recent Supreme Court of Canada decision in *Apotex Inc. v. Sanofi-Synthelabo Canada Inc.* 2008 SCC 61, anticipation and obviousness are related concepts in that they both require an examination of the prior art, but that prior art must be treated differently. Anticipation or lack of novelty requires the Court to examine whether the claimed invention has already been disclosed to the public by a single disclosure in such a way as to enable it to be put into practice. Obviousness (or lack of invention) requires that the Court consider a number of disclosures that would have been known to or found by a person skilled in the art to determine whether an inventive step has been made.

[59] In the present proceeding, Novopharm relies upon two pieces of prior art: United States Patent No. 4,418,068 ('068 patent) which was referred to at page 1 of the '399 patent at issue and an article by Jones et al., also referenced at page 1 of the '399 patent as published in the *Journal of Medicinal Chemistry 2718),* 1057-1066 (1984) which is the Jones Article. Both pieces of prior art were published sufficiently early so as to be applicable from a date point of view. It is

acknowledged that the Jones who is an author of the article is also the named inventor of the ’068 patent.

[60] The ’068 patent was granted to the Respondent Lilly US naming Jones as an inventor. Jones and the other authors of the Jones Article appear from what is said at the first page of that article to be members of the research laboratory of Lilly US..

THE ’068 PATENT

[61] The ’068 patent, as acknowledged at page 1 of the ’399 patent, discloses raloxifene hydrochloride that is said to show promise as a pharmaceutically – active agent. The ’068 patent discloses how to make a number of compounds including raloxifene hydrochloride. Examples 16 and 18 are of particular interest in this regard. Example 16 discloses how to make a crude raloxifene hydrochloride and Example 18 discloses how to purify it:

EXAMPLE 16

> *6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl] benzo[b]-thiophene hydrochloride. A mixture of 1.5 g. of 4-(2-piperidinoethoxy)benzoic acid, hydrochloride, 20ml. of chlorobenzene, 3ml. of thionyl chloride and 2 drops of dimethylformamide was stirred at 75°-79° for 2 hours, to prepare the corresponding acid chloride. Vacuum was then applied, and the temperature dropped to 65°. Distillation was continued until the pot temperature was 90°. Twenty ml. of additional chlorobenzene was added, and the mixture was redistilled to a pot temperature of 90°, and was then cooled. To the mixture was added 15ml. of dichloromethane, 1.35g. of 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl] benzo[b]-thiophene, 5 g. of aluminum chloride and 15 ml. of additional dichloromethane. The mixture was stirred at 27°-29° for 90 minutes, and then 1.6 ml. of ethanethiol was*

added. The mixture was stirred with cooling to maintain it at or below 35°. After 30 minutes, the mixture was worked up as described in Example 8 above, except that only 18 ml. of tetrahydrofuran and of water were used, to obtain 2.6 g. of the crude desired product, m.p. 217°, which was found to be substantially identical to the product of Example 8 by nmr and thin layer chromatography.

…

EXAMPLE 18

Purification of 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl] benzo[b]-thiophene hydrochloride.

Two hundred g. of crude 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl] benzo[b]-thiophene hydrochloride, typical of the product of Example 16 above, was added to 4400 ml. of methanol and 60 ml. of deionized water in the 3-liter flask. The slurry was heated to reflux, whereupon most of the crude product went into solution. The remaining solid was removed by filtration under vacuum, using a filter aid pad. A distillation head was then attached to the flask, and solvent was distilled off until the volume of the remaining solution was about 1800ml. The heating mantle was slowly then turned off, and the solution was cooled very slowly overnight, with constant stirring. The crystalline product was then collected by vacuum filtration, and the flask was washed out with filtrate to obtain all of the product. The crystals were washed on the filter with two 100 ml portions of cold (below 0°C.) methanol, and the washed product was dried at 60°C under vacuum to obtain 140g. of dried product.

The product was slurred in 3000ml. of methanol and 42ml. of water, heated to reflux and cooled very slowly. The product was filtered and dried, as above to obtain 121 g. of highly purified product, m.p. 259°-260°C.

[62] The ’068 patent at column 28 and following describes a number of tests which were conducted using compounds such as those prepared by these Examples. No tests were conducted

on humans however at column 38, lines 46 to 49 the tests are said to be "clearly predictive" of beneficial effects in humans. No problems related to any impurity in the compounds are reported.

[63] I accept the analysis provided by Dr. Tidwell at paragraphs 57 to 61 of his affidavit as setting out the steps involved in Examples 16 and 18 of the '068 patent with the caution that one must keep open mind as to what is meant by the word "purified" in respect of the end product. I repeat those paragraphs:

> *57. In my opinion, a person skilled in the art who reviewed the 268 Patent would understand that the synthesis and crystallization described in Examples 16 and 18 produced Purified Raloxifene. My reasons for this conclusion are as follows.*
>
> *58. The crystallization step of Example 18 begins with the crude raloxifene produced by the process of Example 16 of the 068 Patent. Example 16, which incorporates Example 8, describes a process for synthesizing crude raloxifene hydrochloride that, in layman's term, involves the steps of Activation, Distillation, Acylation, Deprotection, Purification and Collection.*
>
> *59. The steps of Example 16 (the "Example 16 Steps") are as follows:*
>
> > *(a) Activation of the substituted benzoic acid by conversion using thionyl chloride and heating in chlorobenzene solvent to form an acid chloride. Activation is required to facilitate the bonding of the benzoic acid to the benzothiophene.*
> >
> > *(b) Distillation under vacuum to remove chlorobenzene solvent which would otherwise remain as an impurity in the final product. Distillation is a method of purification.*
> >
> > *(c) Acylation of the acid chloride with the benzothiophene using aluminum chloride as the catalyst and dichloromethane as the solvent. Acylation is the process of creating a chemical bond*

> *between the acid chloride and the benzothiopherie. This step would result in aluminum salt impurities and possible organoaluminum impurities due to the use of aluminum chloride.*
>
> *(d) Deprotection by the addition of aluminum chloride, ethanethiol, and dichloromethane to the product of step (c) and stirring the mixture. The addition of aluminum chloride would result in further formation of aluminum salt impurities. Deprotection is the step required to remove methoxy methyl groups, which can create sulfur-containing impurities.*
>
> *(e) Purification by addition of tetrahydrofuran, aqueous hydrochloric acid, water and aqueous sodium chloride, followed by precipitation. This is a crystallization step involving dissolution of the compound in an aqueous solvent and slow cooling to allow the precipitation of the compound.*
>
> *(f) Collection of the compound precipitate by filtration, washing and drying. This compound is what I called crude raloxifene.*

60. Example 18 of the 068 Patent provides for the further purification of the crude raloxifene hydrochloride by a recrystallization process that includes the steps of Heating/Filtration, Distillation, Crystallization, Collection and Repetition.

61. The steps of Example 18 (the "Example 18 Steps") are as follows:

> *(g) Heating the crystalline compound obtained from Example 16 in methanol and water, and filtration of the resulting solution. Methanol is a good solvent for raloxifene. Filtration removes any insoluble impurities, such as any aluminum salts and organoaluminum impurities that may have been present.*
>
> *(h) Distillation to partially remove the methanol, water and other volatile impurities.*

> *(i) Crystallization by slowly cooling the solution with stiffing, which leans to precipitation out of crystalline raloxifene hydrochloride.*
>
> *(j) Collection of the crystalline product by filtration followed by washing and drying.*
>
> *(k) Repeat steps (g) (without filtration) through (j), that is, perform a further recrystallization which would further remove any impurities.*

The Jones Article

[64] Jones is the named inventor of this ’068 patent. He, together with others, all of whom appear to be members of the Lilly US research laboratory, wrote an article published in the *Journal of Medicinal Chemistry*, 27(8), at pages 1057-1066 in 1984-the “Jones Article”. This Article is acknowledged at page 1 of the ’399 patent. The ’399 patent, at page 1, further acknowledges that this paper discloses a process for synthesizing raloxifene but claims that there are purity problems with the compounds produced.

[65] The Jones Article at pages 1065 and 1066 discloses a process for synthesizing what it calls Compound 50. This compound is acknowledged to be raloxifene hydrochloride. This compound was tested on rats as reported at page 1066 of the article as to effects on mammary tumors and the results set out at Tables IV and V on page 1062.

[66] I will not set out the process for making raloxifene hydrochloride as set out in the Jones’ article because of its length and the complexity of the data. I accept Dr.Tidwell’s description of the

process as set out in paragraphs 71 to 74 of his affidavit and I note his conclusion in paragraph 75 that the processes in the Jones Article and the '068 patent are for all intents and purposes the same:

> *71. The Jones Article sets out the details of the preparation of raloxifene hydrochloride (called "Compound 50" in the Jones Article) on pages 1065-6. The synthetic process for preparing Compound 50 (the 'Compound 50 Process") involves the use of chlorobenzene, aluminum chloride and ethanethiol as set out in the 068 Patent. The Compound 50 Process essentially includes steps (a) to (f) of the Example 16 Steps[1] described above and therefore, necessarily includes both purification steps in Example 16. I note that the lead author for the Jones Article (Charles Jones of Eli Lilly and Company) is the named inventor for the 068 Patent.*
>
> *72. There is one additional step described in the Jones Article for the Compound 50 Process that is not in Example 16. It involves the further addition and removal of chlorobenzene, in this case for the purpose of removing thionyl chloride. In my view, this additional step would not impact the purity of Compound 50 with regards to chloroberizene, aluminum salts, organoaluminum impurities, and sulfur-containing (odor causing) impurities.*
>
> *73. The Jones Article reports that crude raloxifene hydrochloride in the form of a THF solvate of Compound 50 is obtained from the Compound 50 Process. This THF solvate is called "crude 50" and was reported as having a melting point of 217°C.*
>
> *74. There is then a recrystallization step where "pure 50" or Compound 50 is obtained. This recrystallization step was done from methanol and water as solvent. This is identical to the recrytallization (without filtration) described in the Example 18 Steps in the 068 Patent.*
>
> *75. As the Compound 50 Process in the Jones Article is for all intent. and purposes the same as the processes described in the Examples 16 and 18 Steps of the 068 Patent, it is my opinion that Compound 50 is the same crystalline raloxifene hydrochloride as the 068 Raloxifene Hydrochloride.*

ANTICIPATION AND OBVIOUSNESS – LEGAL PRINCIPLES

[67] The legal principles in Canada respecting anticipation and obviousness were recently considered by the Supreme Court of Canada in *Apotex Inc. v. Sanofi-Synthelabo Canada Inc.*, *supra*. Subsequent to the release of that decision, I reviewed the law particularly as to anticipation in *Abbott Laboratories v. Canada (Minister of Health)*, 2008 FC 1359. The Federal Court of Appeal within the last few weeks has released its decision in *Apotex Inc. v. Pfizer Canada Inc.*, 2009 FCA 8 where it considered the decision of the Supreme Court of Canada in the context of obviousness.

[68] In *Sanofi*, Rothstein J. for the Supreme Court wrote that, with respect to anticipation, there must be in the prior art under consideration both a disclosure of what is claimed in the claims at issue, and sufficient information given so as to enable what is disclosed to be put into practice by a person skilled in the art. At paragraph 30, he wrote:

> ***30*** *Two questions now must be answered: (1) what constitutes disclosure at the first stage of the test for anticipation, and (2) how much trial and error or experimentation is permitted at the enablement stage?*

[69] In the particular circumstances of *Sanofi* the Supreme Court had to consider what is sometimes called a selection patent where there has been a disclosure of a genus of compositions but the patent at issue selected a member from the genus because it had special advantages. In that context, Rothstein J.'s commentary as to disclosure at paragraph 32 of *Sanofi* can be best understood:

> ***32*** *In the context of disclosure as explained in* Synthon, *"the absence of the discovery of the special advantages" to which Lord*

> *Wilberforce was referring in* Witsiepe's *means that the genus patent does not disclose the special advantages of the invention covered by the selection patent. Where there is no such disclosure, there is no discovery of the special advantages of the selection patent as compared to the genus patent, and the disclosure requirement to prove anticipation fails. At this stage, the person skilled in the art is reading the prior patent to understand whether it discloses the special advantages of the second invention. No trial and error is permitted. If in reading the genus patent the special advantages of the invention of the selection patent are not disclosed, the genus patent does not anticipate the selection patent.*

[70] Rothstein J. then turned to enablement and drew up a non-exhaustive list of four factors that could be considered in determining whether what has been disclosed has also been enabled that is, has enough information been given to enable a skilled person to put that which has been disclosed into practice. He wrote at paragraph 37:

> ***37*** *Drawing from this jurisprudence, I am of the opinion that the following factors should normally be considered. The list is not exhaustive. The factors will apply in accordance with the evidence in each case.*
>
> > *1. Enablement is to be assessed having regard to the prior patent as a whole including the specification and the claims. There is no reason to limit what the skilled person may consider in the prior patent in order to discover how to perform or make the invention of the subsequent patent. The entire prior patent constitutes prior art.*
> >
> > *2. The skilled person may use his or her common general knowledge to supplement information contained in the prior patent. Common general knowledge means knowledge generally known by persons skilled in the relevant art at the relevant time.*
> >
> > *3. The prior patent must provide enough information to allow the subsequently claimed invention to be performed without undue burden.*

> *When considering whether there is undue burden, the nature of the invention must be taken into account. For example, if the invention takes place in a field of technology in which trials and experiments are generally carried out, the threshold for undue burden will tend to be higher than in circumstances in which less effort is normal. If inventive steps are required, the prior art will not be considered as enabling. However, routine trials are acceptable and would not be considered undue burden. But experiments or trials and errors are not to be prolonged even in fields of technology in which trials and experiments are generally carried out. No time limits on exercises of energy can be laid down; however, prolonged or arduous trial and error would not be considered routine.*
>
> *4. Obvious errors or omissions in the prior patent will not prevent enablement if reasonable skill and knowledge in the art could readily correct the error or find what was omitted.*

[71] I reviewed this decision in *Sanofi* and other current cases in *Abbott*, *supra* and drew up a list of considerations respecting anticipation to which counsel for both the Applicants and Respondent Apotex have ascribed in the present case. I summarized at paragraph 75:

> ***75*** *To summarise the legal requirements for anticipation as they apply to the circumstances of this case:*
>
> *1. For there to be anticipation there must be both disclosure and enablement of the claimed invention.*
>
> *2. The disclosure does not have to be an "exact description" of the claimed invention. The disclosure must be sufficient so that when read by a person skilled in the art willing to understand what is being said, it can be understood without trial and error.*
>
> *3. If there is sufficient disclosure, what is disclosed must enable a person skilled in the art to carry out*

> *what is disclosed. A certain amount of trial and error experimentation of a kind normally expected may be carried out.*
>
> *4. The disclosure when carried out may be done without a person necessarily recognizing what is present or what is happening.*
>
> *5. If the claimed invention is directed to a use different from that previously disclosed and enabled then such claimed use is not anticipated. However if the claimed use is the same as the previously disclosed and enabled use, then there is anticipation.*
>
> *6. The Court is required to make its determinations as to disclosure and enablement on the usual civil burden of balance and probabilities, and not to any more exacting standard such as quasi-criminal.*
>
> *7. If a person carrying out the prior disclosure would infringe the claim then the claim is anticipated.*

[72] Turning to the question of obviousness, the Supreme Court reviewed a number of authorities and found the restated *Windsurfing* questions to be a useful approach. At paragraph 67 of *Sanofi* Rothstein J. wrote:

> ***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, [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.]*

[73] As to the fourth issue which can be characterized as the "obvious to try" issue, Rothstein J. adopted the words of Jacob L.J. in *Saint-Gobain PAM SA. v. Fusion Provida Ltd.*, [2005] EWCA Civ 177 at paragraph 35, that is, was it "more-or-less self evident" that what is being tested ought to work. Rothstein J. wrote at paragraphs 65, 66, 69 and 70:

> ***65*** *In Saint-Gobain PAM SA v. Fusion Provida Ltd., [2005] EWCA Civ 177, 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.*

…

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] The Federal Court of Appeal in *Pfizer* reviewed a decision of this Court that had been given before the Supreme Court had released its decision in *Sanofi*. The issue was whether in this Court the Judge has applied the appropriate test. The Federal Court of Appeal held that the appropriate test had been applied. At paragraphs 36 and 37, Noel JA. for the Court wrote:

> *[36]It is apparent from the above review that the Federal Court Judge throughout his analysis looked for more than possibilities understanding that mere possibilities were not enough, and that the prior art had to show more than that. His appreciation of the matter is summed up and further demonstrated by his concluding remarks (Reasons, para. 125):*
>
> > *Although there was a significant amount of evidence indicating that cGMP PDE inhibitors should be further explored with regards to the treatment of ED in the months leading up to the Pfizer discovery, the evidence does not in my view establish that the solution taught by the patent was obvious at the time. At best there was speculation, which in hindsight proved to be correct, that PDE5 inhibitors might treat impotence. Experiments with zaprinast, a cGMP PDE inhibitor, had been performed but in an effort to understand how the erectile process works, not how to treat ED.*
>
> *[37] In so holding, the Federal Court Judge drew the line precisely where the Supreme Court drew it in Sanofi-Synthelabo when it held that (para. 66) "the mere possibility that something might turn up is not enough".*

THE JONES ARTICLE – WAS IT PROPERLY CITED FOR ANTICIPATION OR OBVIOUSNESS ?

[75] Before embarking on a detailed consideration of anticipation it is important to look at just what Novopharm said as to anticipation in its Notice of Allegation. This is set out at pages 44 and 45 of the Notice, which in its relevant portion said:

> *Each of GB 2,097,288 ("the '788 Patent"), the '036 Patent and the 068 Patent were published prior to the relevant date, and therefore their subject matter had become available to the public as of the relevant date.*
>
> *The '788 Patent (for example, Examples 18 and 20), the '036 Patent (for example Examples 11 and 16) and the 068 patent (for example, Examples 16 and 18) all individually disclosed the subject matter claimed each and every one of the claims of the '399 Patent, therefore each and every one of the claims is invalid pursuant to s. 28.2 of the Patent Act.*
> *For example, the '788 Patent, the '036 Patent and the '068 Patent disclosed the following:*
>
> …
>
> *The claims for the '399 Patent are invalid because the subject matter of these claims was disclosed to the public in each of the '788 Patent, the '036 Patent and the '068 Patent before the relevant date contrary to the requirements of s. 28.2 of the Patent Act.*

[76] The '788 patent was not asserted in evidence or argument by Novopharm. It appears to be similar to the '068 patent and does not need to be considered further. The Jones Article however was never cited by Novopharm as a basis for anticipation.

[77] Novopharm's counsel, in oral argument, asserted that the failure to mention the Jones article in dealing with anticipation was simply a minor procedural argument and that the Applicants were at all times aware that this article was in play since it was raised in respect of obviousness.

[78] The jurisprudence in this Court has evolved to the point where it has established that a second party has an obligation in its Notice of Allegation to raise all the issues and relevant facts and law upon which it relies and set this out in clear and unequivocal terms such that the first party

will know exactly the case that it will have to meet should it wish to commence proceedings under the *NOC Regulations*. In this regard I stated in *Brystol-Myers Squibb Canada Co. v. Apotex Inc.*, 2009 FC 137 at paragraph 130 in reliance upon Stone JA. in *AB Hassle v. Canada (Minister of Health and Welfare)* (2000), 7 C.P.R. (4TH) 272:

> *[130]A Notice of Allegation is intended to be fulsome, putting the first party on notice as to the allegations made and the factual and legal basis for those allegations. The intent is that the entire factual basis upon which a second person relies is set out with particularity. The second person assumes the risk if the notice is incomplete. I quote from the reasons of the Federal Court of Appeal given by Stone JA. in AB Hassle v. Canada (Minister of Health and Welfare), previously referred to in these reasons when I was dealing with the disclaimer issue. He wrote at paragraph 21and 23:*
>
> > ***21*** *In my view, all of these considerations suggest that a second person must do what, in fact, paragraph 5(3)(a) requires, i.e. set forth in the detailed statement "the legal and factual basis" for the paragraph 5(1)(b) allegation and to do so in a sufficiently complete manner as to enable the patentee to assess its course of action in response to the allegation. See Pharmacia Inc. v. Canada (Minister of National Health and Welfare) (1994), 58 C.P.R. (3d) 209 (F.C.A.), per Strayer J.A. at 216. An examination of the detailed statement in issue is thus required in order to determine whether it measures up to this requirement with respect to the allegation that the '693 and '891 Patents are not valid for obviousness.*
> >
> > …
> >
> > ***23*** *The respondent suggests that the list of prior art in the detailed statement was not intended to be exhaustive, hence the presence of the word "including", so that the way was left open to add to that list in the section 6 proceeding. I am of the view, however, that paragraph 5(3)(a) does not contemplate such possibility. The intent appears to be that the entire factual basis be set forth in the statement rather than be revealed piecemeal when*

> *some need happens to arise in a section 6 proceeding. This Court has cautioned persons in the position of the respondent that they assume a risk that a particular allegation may not be in compliance with the Regulations and that the deficiency cannot be cured by the Court in a section 6 proceeding. In Bayer AG v. Canada (Minister of National Health and Welfare) (1995), 60 C.P.R. (3d) 129 (F.C.A.), Strayer J.A. stated, at 133-134, in reference to the decision of this Court in Pharmacia Inc. v. Canada (Minister of National Health and Welfare) (1994), 58 C.P.R. (3d) 207:*
>
> > *The order appealed from here was made before this court had had occasion to clarify certain issues arising out of the Regulations. In particular, this court in Pharmacia Inc. v. Canada (Minister of National Health and Welfare)...[since reported at 58 C.P.R. (3d) 207]...stated the following [at p. 209]:*
> >
> > > *It seems to us that while a notice of allegation does play an important role in the ultimate outcome of litigation of this nature, it is not a document by which the judicial review application may be launched under s. 6 of the regulations. That document was put in as a piece of evidence by the appellants; it originated with the application filed before the Minister. Because it is not a document that was filed with the court but with the Minister, in our view the notice of allegation is beyond the reach of the court's jurisdiction in a judicial review proceeding. That being so, the court, in our opinion, lacks jurisdiction to strike out the notice of allegation.*

This clearly means that the court has no jurisdiction to make orders concerning the filing of notices of allegation or requiring them to be perfected in some way. The principle is that, by the

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

[79] Therefore I find that Novopharm cannot rely, for purposes of its argument as to anticipation, on the Jones Article.

[80] The situation is different when it comes to the matter of obviousness. Novopharm says in respect of obviousness at page 45 of its Notice of Allegation, as to the ’399 patent:

> *All the claims of the ’399 Patent are invalid on the basis that the subject matter of these claims would have been obvious to a person skilled in the art at the relevant date contrary to s. 28.3 of the Patent Act.*
>
> *Pursuant to s. 28.3(b) of the Patent Act, a claim is invalid if the subject matter of that claim would have been obvious to a person skilled in the art in view of public information disclosed by a person other than the applicant before the claim date. For purposes of this Notice of Allegation only, Novopharm alleges that the claim date for the ’399 Patent is September 19, 1994 (the filing date of the earliest priority document), and that the subject matter claimed would have been obvious to a person skilled in the art of that date. If the claim date is found to be the filing date of the application in Canada, namely, September 15, 1995, then Novopharm alleges that the subject matter claimed have also been obvious to the person skilled in the art of that date.*
>
> *Attached as Appendix “D” to this letter is a list of examples of Prior Art references relevant to the ’399 Patent. All of these Prior Art references were available to the public before the applicable claim*

> *date, and therefore qualify as disclosures by another in accordance with subsection 28.3(b) of the Patent Act. All the references listed in Appendix "D" would have come to the attention of the person skilled in the art doing a diligent search of the prior art at the claim date.*
> *As of the applicable claim date, the common general knowledge known in the art and the teachings of the example references listed in Appendix "D" included the following:*
>
> …

[81] Among the prior art references listed is Appendix "D" is the Jones Article as item 16. Thus the Jones Article has been put into play by Novopharm in respect of the matter of obviousness, even if not in respect of the matter of anticipation.

ZEROING IN ON THE MATTERS IN CONTENTION

[82] The real matters in contention can be described as:

1. Does the '068 patent disclose and enable the invention as claimed in the '399 patent?
2. Do the '068 patent and Jones Article taken together with the common general knowledge that a person skilled in the art would be expected to have as of the relevant date make the invention as claimed in the '399 patent more-or-less self evident?

[83] The Applicant has described the invention as claimed in the '399 patent in the following manner in its first Memorandum of Fact and Law:

> *4. The inventors wished to overcome certain problems relating to the existing process to make raloxifene hydrochloride, described as follows in the '399 Patent.*

> *"U.S. Patent No. 4,418,068 describes 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2- piperidinoethoxy) benzoyl] benzo [b]-thiophene hydrochloride, known as raloxifene hydrochloride, which has shown particular promise as a pharmaceutically-active agent. Unfortunately, this compound has proven extremely difficult to purify. Particular problems have arisen due to solvent contamination. For instance, the process described in the Journal of Medicinal Chemistry, 27(8), 1057-1066 (1984), for synthesizing raloxifene suffered from the serious shortcoming that it produced a solvated compound contaminated with chlorobenzene, a known carcinogen.. Further, other processes described in the literature utilized a classical aluminum chloride-catalyzed Friedel-Crafts acylation. The product of these processes contain aluminum contaminants and various thioester by-products; which are difficult to remove. Also, the product of these literature processes has an unpleasant residual thiol or sulfide odor."*
>
> *'399 Patent, AR Tab 8, page 190.*

> *5. By changing the process for making raloxifene hydrochloride in an attempt to overcome these problems the inventors serendipitously invented a novel non-solvated crystal form defined in the claims by an X-ray diffraction pattern including 41 data points. This X-ray diffraction pattern is essentially a fingerprint uniquely defining the new crystal form.*

[84] This is not very different from the position taken by Novopharm as to the inventive concept in its Memorandum:

> *93. The inventive concept of the 399 Raloxifene, being the 95% pure crystalline non-solvate, free from the contaminating impurities said to exist in the prior art raloxifene, and identified by the 399 XRPD.*

[85] The only real difference between the two positions is that Novopharm states that the concept includes freedom from impurities; the Applicant does not mention this. In the ’399 patent the concept of freedom from impurities is not included in claim 1 but only the later claims.

[86] Turning to anticipation and the ’068 patent, the Applicant in its Memorandum concedes that Examples 16 and 18 disclose “*a highly purified crystal form of raloxifene hydrochloride*”. The Applicants position is however, that it is not disclosed whether such form is solvated or not or whether it has the particular X-ray pattern of Claim 1. In its first Memorandum, the Applicant says:

> *27. The experts for both parties agree that Example 16 discloses crude raloxifene hydrochloride that may or may not be solvated. Similarly, experts for both sides agree that, on its face, Example 18 discloses a highly purified crystal form of raloxifene hydrochloride that may or may not be solvated. …*
>
> *28. The most that can be said about the prior art submitted by Novopharm is that it discloses a process to produce the compound raloxifene hydrochloride, but there is no specific disclosure of producing a non-solvated crystalline form of raloxifene hydrochloride identified by the X-ray diffraction pattern in Claim 1 of the ’399 Patent.*

[87] I will approach the question of anticipation by the ’068 patent and, in particular, whether the ’068 patent both discloses and enables what is claimed in the ’399 patent without any more than routine trial and error experimentation from three standpoints:

1. What does Lilly US, the patentee of both of the ’068 patent and the ’399 patent at issue tell us;
2. What do the experts say based on their theoretical analysis; and
3. What do the Ferrari/Chyall experiments tell us?

1. <u>WHAT DOES LILLY US SAY?</u>

[88] Lilly US is the patentee as named in both of the ’068 and ’399 patents. The ’068 patent appears to be the first to identify raloxifene hydrochloride as a useful pharmaceutical. At column 1 line 55 to column 2 line 11 the ’068 patent identifies three groups of compounds said to be under investigation for pharmaceutical utility. The third group, benzathiophenes, are considered to be more effective with fewer side effects.

[89] At column 2, lines 51 to 56 of the ’068 patent the invention is described in terms that we now call raloxifene hydrochloride:

> *This invention provides a single benzothiophene compound and the physiologically acceptable esters and ethers which are formed on one or both of the hydroxyl groups of compounds. The invention also provides physiologically acceptable salts of the compound in any of its forms.*

[90] A number of examples are provided as to how to prepare raloxifene hydrochloride by different methods. One such method is that of Example 8, another is that of Example 16. The method of Example 16 using the quantities of starting materials set out is said to yield “*…2.6g of the crude desired product…*”. That product is said to be “*…substantially identical to the product of Example 8 by nmr and thin layer chromatography*”.

[91] Example 18 of the ’068 patent starts with 200 g. of the crude product “*typical of the product of Example 16*”. Therefore either a number of Example 16 runs were made or Example 16 was scaled up to produce 200g. of “crude” product. Example 18 purifies the product and produces a crystalline product said to be “*highly purified*”. It is worth setting out Example 18 again:

EXAMPLE 18

> *Purification of 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl] benzo[b]-thiophene hydrochloride.*
>
> *Two hundred g. of crude 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl] benzo[b]-thiophene hydrochloride, typical of the product of Example 16 above, was added to 4400 ml. of methanol and 60 ml. of deionized water in the 3-liter flask. The slurry was heated to reflux, whereupon most of the crude product went into solution. The remaining solid was removed by filtration under vacuum, using a filter aid pad. A distillation head was then attached to the flask, and solvent was distilled off until the volume of the remaining solution was about 1800ml. The heating mantle was slowly then turned off, and the solution was cooled very slowly overnight, with constant stirring. The crystalline product was then collected by vacuum filtration, and the flask was washed out with filtrate to obtain all of the product. The crystals were washed on the filter with two 100 ml portions of cold (below 0^oC.) methanol, and the washed product was dried at 60^oC. under vacuum to obtain 140g. of dried product.*
>
> *The product was slurred in 3000ml. of methanol and 42ml. of water, heated to reflux and cooled very slowly. The product was filtered and dried, as above to obtain 121 g. of highly purified product, m.p. 259^o-260^oC.*

[92] The product was then tested in a number of ways, including, as reported in the ’068 patent, on laboratory animals. No tests on humans are reported. However at column 38 lines 44 to 49 the ’068 patent states that the tests are “*clearly predictive*” of beneficial effects in humans:

> *The tests which have been applied to a representative compound of this invention were carried out in standard laboratory animals, as described above. The tests which have been applied to the compounds are believed to be clearly predictive of beneficial effects in humans, in humans, based on the effects in laboratory animals.*

[93] Thus the ’068 patent provides a method to make crude raloxifene hydrochloride (Example16) and how to purify the crude into a “*highly purified*” crystal form of raloxifene

hydrochloride (Example 18). That product is "*clearly*" predicted to have pharmaceutical utility in humans. There is no suggestion in the'068 patent as to impurities or any problems arising from impurities.

[94] As will become important in considering the evidence of Chyall, it must be presumed that the patentee of the '068 patent, Lilly US, in providing examples, including Examples 16 and 18, is providing information that is accurate and sufficient so that a person skilled in the art can put those examples into practice.

[95] Now turning to the '399 patent, it claims to be an improvement on the '068 patent processes and so-called "other processes" for producing raloxifene hydrochloride in that it is alleged that undesirable impurities occur in the '068 processes as well as the "other processes". To repeat again what is said at page 1 of the '399 patent:

> *U.S. Patent No. 4,418,068 describes 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl] benzo[b]-thiophene hydrochloride, known as raloxifene hydrochloride, which has shown particular promise as a pharmaceutically-active agent. Unfortunately, this compound has proven extremely difficult to purify. Particular problems have arisen due to solvent contamination. For instance, the process described in the Journal of Medicinal Chemistry, 27(8), 1057-1066 (1984), for synthesizing raloxifene suffered from the serious shortcoming that it produced a solvated compound contaminated with chlorobenzene, a known cancinogen. Further, other processes described in the literature utilized a classical aluminum chloride-catalyzed Friedel-Crafts acylation. The product of these processes contain aluminum contaminants and various thioester by-products, which are difficult to remove. Also the product of these literature processes has an unpleasant residual thiol or sulphide odor.*

[96] Thus what one is told in the ’399 patent is that the ’068 process has problems; it produces a raloxifene that is contaminated with chlorobenzene. There is a different problem with raloxifene made by “other processes” namely aluminum contamination and sulphide odors.

[97] Claim 1 of the ’399 patent as previously construed requires raloxifene hydrochloride to be in a crystalline form, a criteria met by Examples 16 and 18 of the ’068 patent, which form is non-solvated and has a particular XRPD pattern. Examples 16 and 18 of the ’068 patent are silent as to whether the form is solvated or non-solvated and as what is the XRPD pattern.

[98] Claim 1 does not require any particular purity, claim 2 requires at least 95% purity, claim 3 requires raloxifene hydrochloride of claim 1 or claim 2 that is “substantially free of chlorobenzene” which I have construed to mean less than 5% by weight of chlorobenzene.

[99] Would a person skilled in the art, following the processes of Examples 16 and 18 of the ’068 patent, produce non-sovlated crystalline raloxifene hydrochloride having the particular XRPD pattern and have less than 5% chlorobenzene?

[100] Addressing again the legal criteria that have to be satisfied one must remember that the answer to the above question, on the science, must be that such a product must be produced with no more than the usual trial and error expected of a person skilled in the art. On the evidence I must be satisfied that this will happen on the usual civil burden of proof, the balance of probabilities.

[101] What then is the evidence? It is twofold, one is expert opinion, the other is the testing of Ferrari and Chyall.

2. <u>WHAT DO THE EXPERTS SAY BASED ON THEORY?</u>

[102] Turning to the expert evidence, I prefer the evidence of Tidwell when it comes to a discussion of organic synthesis. Bernstein, the Applicant's expert clearly stressed that he had no claim to expertise when it came to organic synthesis. For instance I cite the following exchange at questions 15 and 221 of Bernstein cross-examination:

> *15. Q. You don't indicate you have specialized in synthetic chemistry but I take it you would have some experience in synthetic chemistry?*
> *A. I am not a synthetic chemist, and I really don't – we really do very, very little synthetic chemistry in my laboratory.*
>
> …
>
> *211. Q, Sure. The first step you are told to take in making compound 50 involves going back to the bottom of 49, and that's the activation of the benzoic acid using thionyl chloride and heating in chlorobenzene for form an acid chloride; is that correct?*
> *A. well, I, I you went through my CV with me, and I did – and I think you asked me about organic chemistry. I was trained as a physical chemist. I really don't do, essentially don't do, I or my students or my group, we don't do any of the organic synthesis. I don't feel really very comfortable talking about the details of the synthetic steps here.*

[103] Thus in determining from the theoretical point of view what Examples 16 and 18 would produce, I prefer the evidence of Tidwell who, as can be seen from his background and experience as set out in paragraphs 2 to 9 of his affidavit, has for his entire professional career been involved in synthesis of this type.

[104] Dr. Tidwell's evidence, particularly at paragraphs 56 to 68 of his affidavit and his vigorous cross-examination particularly at questions 97 through 108, persuades me that a person skilled in the art in looking at Examples 16 and 18 of the '068 would reasonably have expected those processes to yield a non-solvated form of crystalline raloxifene hydrochloride that contained less than 5% by weight of chlorobenzene.

[105] Dr. Bernstein's evidence is to the effect that one doesn't know for certain whether the final product is a solvated or non-solvate and that it "may" be a solvate. His cross-examination was more focused on the Jones Article but the questioning from questions 179 through 208 illustrates the speculative nature of Dr. Bernstein's evidence. I prefer the more positive evidence of Dr. Tidwell.

[106] The remaining question is, even if Examples 16 and 18 produce a sufficiently pure non-solvated crystalline from of raloxifene hydrochloride, does it have the XRPD pattern of claim 1 (and by incorporation, all the other claims)? In this regard the Applicant relies on the evidence of Dr. Bernstein for instance at paragraphs 61 to 64 to assert that one can never know how many different crystal forms may be produced, each with a different XRPD pattern or "fingerprint". This proposition was put the Dr. Tidwell in cross-examination, particularly at questions 149 through 165 in respect of Examples 16 and 18 as well as the Jones Article. He was repeatedly confronted with whether different forms could exist. I am persuaded by his answers that the XRPD of the form produced by Examples 16 and 18 would only be that of claim 1. To quote from his answers to questions 153 to 155:

> *Q. But you would still need to know that the X-ray diffraction pattern of this sample, and I mean Example 18, was done to know that it fell within the scope of Claim 1?*
> *A. I think it is highly probable that this gives the same XRPD as the one in Claim 1. And so therefore I think it does fall within the scope of Claim 1.*
>
> *Q. You say "highly probable". That is not certain, though. You would need to run the X-ray powder diffraction on the sample that was made by Example 18 and only then would you know for certain; correct?*
> *A. Well, I am certain it gives the same XRPD. If I am asked to compare two XRPDs, then obviously I would have to have them both in front of me. But the seen no reason to imagine this would not give that same XRPD.*
>
> *Q. But it is possible that it gives a different one?*
> *A. I would say it is barely conceivable.*

[107] Therefore I find, upon review of the evidence of the experts for the parties, Dr. Bernstein and Dr. Tidwell that, on the usual civil burden, it has been proved, using the legal tests established in *Sanofi* that the '068 patent, in particular Examples 16 and 18 discloses and enables a crystalline form of non-solvated raloxifene hydrochloride which has less than 5% chlorobenzene and no detectible aluminum or organic aluminum impurities or odor, which has the XRPD pattern of claim 1 (and all other claims) of the '399 patent.

EXPERIMENTS OF CHYALL AND FERRARI

[108] I turn now to the experiments of Dr. Chyall and Dr. Ferrari.

[109] Dr. Chyall is an employee of an independent research and analytical company, Aptuit, located in or near Purdue University in Indiana. He was asked by a United States Attorney,

Feldstein, who was apparently acting for Lilly US, to conduct experiments intended to replicate Examples 16 and 18 of the ’068 patent. This was done well before these present proceedings were instituted. The purpose in doing such experiments at the time is unclear. Apparently Chyall ran several experiments intended to replicate Example 16 and was unable to produce any material with a result other than what he described as a “goo”. Therefore he was unable to proceed to Example 18.

[110] When Chyall got the “goo” he washed the spatula he was using to mix the goo with 2-propanol which is a material that he had in his laboratory wash bottle. Chyall got a white solid as a result. He reported this to Feldstein who apparently told him not to deviate from the procedure. The goo and white solid were discarded and never analyzed. I refer in particular to questions 172 to 184 of his cross-examination. He said this in answer to question 178:

> *A. Here is what was going through my head at the time of doing this experiment.*
>
> *I am confronted with this thing that just has not worked. I have this messy spatula, and in the process of cleaning it, I get solids, which is sort of what I was trying to do here, quite by accident. I save the solids, and this does open up a possibility if I am going to invent a way to make raloxifene hydrochloride, but at the same time, I would have to say there is nowhere in Example 16 that says use 2-propanol if you get a goo.*
>
> *Therefore, I consider this to be a deviation from the patent. That was also told to me by Mr. Feldstein.*

[111] It is curious that Lilly US not only in the ’068 patent, but through the Jones Article, represents to the public that it has a workable process to make raloxifene hydrochloride, yet Chyall apparently is unable to do so. Even when he gets a “goo” or white solid he is instructed by a lawyer

acting for Lilly US to get rid of it and no analysis is conducted. Is Lilly US now saying to this Court that its ’068 patent exemplifies a process that does not work?

[112] Dr. Ferrari makes some observations in his affidavit as to why Dr. Chyall’s experiments turned out as they did, for instance measuring temperature in a certain way. At best this is speculative. I place little weight on Chyall’s experiments for two reasons, the first is that Lilly US appears to be contradicting itself, the second is that the experiments were controlled by a lawyer representing Lilly US who seems to have precluded testing or retention of the goo or white material for unknown reasons. It would have been more credible if the material had been tested or at least saved rather than discarded.

[113] Dr. Ferrari conducted experiments intended to replicate Example 16 and 18 on a larger scale. He ended up with material which was tested by Dr. Stradi by XPRD which indicated that the material had, with reasonable comparability, the XRPD of claim 1.

[114] The Applicant has been critical of Dr. Ferrari’s work for a number of reasons including a suspicion of bias which I have already dealt with, the fact that his notebook as to the experiments contain little more than a recitation of the Examples themselves, and the fact that his testing was carried out on a larger scale, about a ten fold increase. As to the notebook matter, I do not consider this matter to be significant. How a notebook is kept is a highly individualized matter and Applicant’s counsel cross-examined Dr. Ferrari at length without establishing anything of note that would cast doubt as to what Dr. Ferrari did. As to the larger scale, the matter was put to Dr. Ferrari

on cross-examination; he reported that the scale does not change the result. In an answer to a question put at page 29 of the transcript of his cross-examination he said at pages 29 and 30:

> *Q. Would you agree with me that, in general terms, changing the scale of an experiment can change the result?*
>
> *A. I would say not. It was hopeful that this does not occur if you use the same type of equipment. I'll give you an example. If you use the container of a certain shape and a certain capacity and you use the same kind of materials and reactors and if the process that is used is a good one, "robust" is the technical term we use in this case, I do not expect results that are totally different between one experiment and the other. There might be differences in the yield but these differences would not determine the success or the failure of the experiment itself.*
>
> *If I may, I would like to add that I, myself, have personally checked that, in the case of example 16, changing scales in the batch size of the reaction did not lead to such differences as to state that one of the two experiments was successful and the other wasn't.*

[115] Dr. Chyall in cross-examination was not certain as to the effect of a scale up, he said he really did not know. At questions 247 and 248 he answered:

> *Q. If it works at a tenfold scale, it ought to work at the smaller scale as well; isn't that correct?*
>
> *A. It is hard for me to – I presume we are speaking about Example 16 here?*
>
> *Q. Correct.*
>
> *A. It is hard for me to know. I am still troubled by the fact that at the scale that I ran it did not work, an issue of scale that I raised here in the affidavit. If there is some other issue that I have not explored by yet another permutation, it could be that as well.*
>
> *I really do not know.*

[116] I am satisfied on a balance of probabilities, that Dr. Ferrari's work is a reasonable replication of Examples 16 and 18 of the '068 patent and that he obtained a highly purified crystalline raloxifene hydrochloride as set out in paragraphs 4 to 7 of his affidavit.

[117] The material obtained by Dr. Ferrari was examined by XRPD by Dr. Stradi. The match between what he found and what is set out in claim 1 of the '399 patent is not exact, but, on the evidence, I find that the match is sufficiently close so as to conclude that the crystal form obtained by Dr. Ferrari is that of claim 1. Dr. Stradi said in answer to a question put to him on cross-examination at page 16 of the transcript:

> *Q. …does that mean that there is at least some chance that they don't match up?*
>
> *A. On the basis of my personal experience, I would say no. On the basis of my experience I can say that, under these conditions, the two crystal structures are the same. The two compounds have the same crystal cell. The small differences that do not allow the fit to occur but neither do these two fit 100 per cent, so to say, the small differences are due to experimental and instrumental conditions which are different, different experimental and different instrumental conditions. I have analyzed tens of thousands of these cases and my experience allows me to say that the two crystal structures are the same also on the basis of those data. And then, in order to be at piece with my conscience, I wanted to carry out an experimental control and this shows that the two crystals are absolutely identical: the one prepared in one way and the one prepared in the other way. The crystals are absolutely the same type and here we have a documentation of the new crystals but this was my problem, totally my problem.*
>
> *Q. So you're telling me there is absolutely no experimental error involved with your experiment?*
>
> *A. No, there's absolutely no experimental error in my experiment.*

[118] Rather strangely Dr. Bernstein declined to answer directly as to whether there was any material difference between Dr. Stradi's XRPD results and those of claim 1, protesting that he only saw the results "*in the last day or two*". At questions 339 to 343 of his cross-examination he answered:

> *339. Q. And Dr. Stradi compared the peak list in the '399 patent with the peak list he obtained from the raloxifene hydrochloride he tested. Do you understand that?*
> *A. Could you point me to where he said that? I assume that is what he did, but I don't recall. As I said, I have had a very brief look at this I haven't had a chance to.*
>
> *340. Q. Paragraph 12?*
> *A. His affidavit?*
>
> *341. Q. His affidavit is at the beginning.*
> *A. Okay, I mean. I compared – You know, I guess that is his judgment. He said he did.*
>
> *343. Q. And gives his opinion that they match; that is his judgment as well?*
> *A. That is his opinion.*
>
> *343. Q. And did you make that comparison, Dr. Bernstein?*
> *A. No. As I said, I only saw this in the last day or two. I haven't had a chance to do that at all.*

[119] I am satisfied that Dr. Stradi's results show that the crystalline form of raloxifene hydrochloride obtained by Dr. Ferrari has the XRPD of claim 1 (and all other claims) of the '399 patent. This evidence, therefore, substantiates that of Dr. Tidwell that Examples 16 and 18 of the '068 patent are sufficient disclosure, and sufficiently enable a person skilled in the art to put into practice, without undue experimentation, a process whereby, crystalline non-solvated form of raloxifene hydrochloride with less than 5% by weight chlorobenzene having the XRPD of the claims, is produced.

[120] Therefore I find that, on the evidence, Novopharm's allegation that the claims of the '399 patent are anticipated is justified.

OBVIOUSNESS

[121] I have determined that Examples 16 and 18 of the '068 patent constitute a sufficient anticipation of what is claimed in the '399 patent. The '068 patent is not an obscure reference, it is mentioned at the first page of the '399 patent. The '068 patent is clearly directed to raloxifene hydrochloride and is something that clearly would have been found at the relevant time by a person skilled in the art. The same can be said for the Jones Article which simply adds weight to what has been said about '068 patent.

[122] To repeat the restated *Windsurfing* test as endorsed by the Supreme Court of Canada in *Sanofi*, the Court, in considering obviousness, should:

> *(1) (a) Identify the notianal "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; and*
>
> *(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?*

[123] Point 1(a) has already been addressed. The art of which the person would have knowledge includes the ’068 patent and the Jones Article. Something clearly stated in the first page of the ’399 patent.

[124] The inventive concept has already been discussed in these Reasons, a non-solvated form of crystalline raloxifene hydrochloride having a certain XRPD pattern which has less than 5% chlorobenzene and other impurities as produced by a process directed to reduction of unwanted impurities.

[125] The different between the inventive concept and what is disclosed in the‘068 patent and the Jones Article, as well, is nothing.

[126] I am satisfied, if it even needs discussion, that the identification of unwanted impurities and adjustments in the processing of raloxifene hydrochloride and the purification of materials obtained was at all relevant times well within the grasp of a person skilled in the art. In this regard I refer to paragraphs 95 to 102 of the Tidwell affidavit. Dr. Bernstein in his affidavit at paragraphs 60 and following, particularly at paragraph 64 appears to acknowledge that a person skilled in the art would make choices but that the resulting crystal, if any, could not be predicted with any certainty. This may well be true, but it is irrelevant since the ’068 patent as well as the Jones Article, describe and enable a process that produces a crystal form as claimed in the ’399 patent. These claims are anticipated and obvious.

[127] To consider motivation briefly, there is no mention in the ’068 patent or the Jones Article about impurities or any problems associated with them. There is no piece of literature nor any

evidence suggesting that anyone perceived a problem with impurities. Only the ’399 patent says that impurities were a problem. It is reasonable to presume that since Lilly US was the company that discovered raloxifene hydrochloride that it would be the organization that would continue to work on it and improve it.

[128] However not every improvement is an invention. I am satisfied, particularly on the evidence of Tidwell, that adjustments to processes, ingredients and purification were techniques well within the skill of a person skilled in the art at the relevant time to deal with impurities if and when they become a problem. The motivation, if any, was routine.

[129] Novopharm allegation as to invalidity of the ’399 patent for obviousness is justified.

CONCLUSION AND COSTS

[130] I have concluded that Novopharm’s allegations as to invalidity of the ’399 patent for invalidity and obviousness are justified. Therefore the application for prohibition is dismissed.

[131] Novopharm is entitled to its costs to be paid by the Applicant. The parties agreed that I should instruct that costs and disbursement be taxed in a manner similar to what I have done in earlier cases of this type. No costs shall be awarded to or payable by either the Minister or Lilly US, neither of whom actively participated in the proceeding.

[132] Novopharm’s costs shall be assessed at the middle of Column IV. Two counsel, senior and junior, shall be allowed at the hearing and, if present, in conducting cross-examination. Only one

counsel, a senior, is allowed in defending a cross-examination. No costs are allowed for other lawyers, in house or out house, as for students, paralegals or clerical persons.

[133] As I have said in other cases, I am concerned as to excessive fees charged by experts. Novopharm is entitled to tax the fees and disbursements charged by each of Tidwell, Ferrari and Stradi but of no other persons who may have assisted or been involved with them. Those fees and disbursements shall be reasonable and not disproportionate to fees and disbursements charged to the Applicant by its experts. I may be spoken to in this regard in the event a disagreement cannot be resolved.

[134] I would hope, given these instructions, that the qualification of costs can be agreed upon.

JUDGMENT

FOR THE REASONS PROVIDED:

THIS COURT ORDERS AND ADJUDGES that:

1. The motion to remove the evidence of Drs. Ferrari and Stradi and, as a result, Dr. Chyall from the Record is dismissed.
2. The application is dismissed.
3. Novopharm is awarded costs to be paid by the Applicant as assessed in accordance with these Reasons.

"Roger T. Hughes"
Judge

FEDERAL COURT

SOLICITORS OF RECORD

DOCKET:	T-1561-07
STYLE OF CAUSE:	**ELI LILLY CANADA INC. v. NOVOPHARM LIMITED et al.**
PLACE OF HEARING:	Ottawa, Ontario
DATE OF HEARING:	February 16-19, 2009
REASONS FOR JUDGMENT AND JUDGMENT:	Hughes, J.
DATED:	March 23, 2008

APPEARANCES:

Patrick Smith Jeff Mutter	FOR THE APPLICANT ELI LILLY CANADA INC.
Barbara Murchie Trent Horne	FOR THE RESPONDENT NOVOPHARM LIMITED
NO APPEARANCE	FOR THE RESPONDENT THE MINISTER OF HEALTH

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