Date: 20090319

Docket: T-1562-07

Citation: 2009 FC 235

Ottawa, Ontario, March 19, 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

[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. 2,250,191 (the '191 patent).

[2] In a related proceeding heard at the same time (T-1561-07) 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 2,150,399 (the ’399 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 told that this proceeding relates to Canadian patent No. 2,101,356 which was the subject of my decision in another matter cited as 2008 FC 142 and is currently under appeal.

[4] For the Reasons that follow, I find that this application is dismissed with costs to Novopharm. These Reasons were released on a confidential basis to the parties on March 4, 2009. An opportunity was given to the parties to indicate whether any changes should be made to the public version now released. They indicated that no changes were required. I have made small spelling corrections at paragraphs 22 and 25.

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. The *NOC Regulations* refer to this party as the “first person”.

[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. The *NOC Regulations* refer to this party as the "second person".

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

[8] The Respondent Eli Lilly and Company Limited (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. 2,250,191 (the '191 patent). The application for that patent was filed with the Canadian Patent Office under the provisions of the Patent Co-Operation Treaty (PCT) effective March 10, 1997. 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 after October 1, 1989. These provisions may be referred to as the new *Patent Act*.

[10] The application for the ’191 patent was laid open for public inspection on October 2, 1997. 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 March 26, 1996 and April 4, 1996. The ’191 patent will expire 20 years from the date of filing the application in Canada, that is, March 20, 2017. The ’191 patent was issued and granted on October 15, 2005. That date is not particularly important in these proceedings save to indicate that the patent has been issued and granted.

[11] In general, and subject to discussion later, the patent is directed to particle size of a compound known as raloxifene and its salts such as raloxifene hydrochloride (HCl). These compounds are directed, among other things, to the treatment of osteoporosis. Well chosen particle size is said to benefit both bioavailability and control of the manufacturing process.

THE EVIDENCE

[12] 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. I have issued a further Order as to certain of the evidence that is to be maintained as confidential.

[13] The Applicant filed the affidavit evidence of the following witnesses:

- Rubina Luebke, a Regulatory Affairs Associate at the Applicant's company. She provided information as to approval of the Applicant's EVISTA product and exhibited certain product information submitted by the Applicant to Health Canada.
- Dr. Robert O. Williams III, professor of Pharmaceutics at the College of Pharmacy at the University of Texas. He claimed expertise in formulation development optimization and delivery of small organic compounds, peptides and proteins by a variety of technologies. He gave evidence directed to validity.
- Dianne Azzarello, pharmacist, experienced in the preparation and filing of new drug submissions. She formed her own company and deals in the filing of New Drug Submissions and Abbreviated New Drug Submissions with Health Canada. She provided comments as to portions of Novopharm's Notice of Allegation and the Applicant's New Drug Submission for its EVISTA product.
- Mark Feldstein, an American attorney admitted to practice before the US Patent and Trademark Office, employed by the Washington law firm Fennegan Henderson. That firm represents the Respondent Lilly US in litigation in the United States Courts against a company known as Teva. Teva is said to supply Novopharm with product samples of which were produced in the context of the US litigation. Feldstein gave evidence in this regard.
- Amy Ganden, Assistant Laboratory Manager of Particle Technology Labs Ltd. (PTL). This lab analysed samples provided by Feldstein. She provided a report as to the results.

- Dr. David E. Bugay, Managing Director of Aptuit Consulting. He specializes in the analysis of materials in the solid state, particularly pharmaceutical drug substances and dosage forms. He gave evidence on the infringement issue in his affidavit in chief. He provided a further affidavit in reply addressing matters raised by Novopharm's witness Biggs on the infringement issue.

[14] Each of Williams, Ganden and Bugay were cross-examined.

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

- A. Louise McLean, a law clerk in the offices of Novopharm's solicitors. She provided a copy of the Notice of Allegation and copies of the documents referenced in that Notice. She provided a second affidavit respecting the delivery of certain Teva samples.
- Dr. (Professor) Isador Kanfer, a professor at the Faculty of Rhodes University, South Africa, author and editor of texts related to drugs, all of which include the areas of bioavailability, dissolution and absorption of drugs. He addressed issues of validity.
- Mali Kadosh Project Manager of Teva, Israel. He testified as to the dispatch of certain samples to Ms. McLean aforesaid.
- Shirley Zhao, analytical chemist at Dalton Pharma Services. She testified as to the analysis of certain samples provided by Ms. McLean aforesaid.
- Dr. (Professor) Simon Biggs, professor of particle science and engineering at the University of Leeds, U.K. His work includes particle size measurement,

characterization and analysis. He gave evidence as to the infringement issue. Biggs provided a further affidavit in sur-reply.

[16] Each of Kanfer, Zhao and Biggs was cross-examined.

[17] The Minister did not file any evidence and did not 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.

[18] 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.

ISSUES

[19] There are two issues raised in this proceeding: validity and infringement of the '191 patent. As to validity there are two grounds raised:

a. Obviousness; and

b. Lack of utility

[20] A third ground raised by Novopharm as to validity was double patenting. Its counsel advised at the hearing that this ground was dropped.

[21] Novopharm has also alleged that its product will not infringe the claims of the ’191 patent. On this issue certain evidence has been provided that will remain confidential. It was conceded by all Counsel at the hearing that Lilly Canada’s product came within the parameters of at least some of the claims of the ’191 patent. It was also conceded by all Counsel at the hearing that claim 7, which deals with a particular use of the product, is not of concern in these proceedings.

BURDEN OF PROOF

[22] The issue as to who bears the burden of proof in NOC proceedings, where the issue of validity of a patent or infringement of a patent is an issue that I had throught 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.

[23] To be perfectly clear, when I 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.*

[24] 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.*

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

[26] 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 recent 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 CLAIMS

[27] The Supreme Court of Canada has instructed that the Court must first construe the claims at issue before moving to consideration of issues such as validity and infringement of those claims, the

purpose in doing so is to identify what it is in the claims that the inventor considered to be essential. This construction is to be conducted in a purposive manner so as to endeavour to be fair to both the patentee and the public of the decision of Binnie J. for the Court in *Whirlpool Inc. v. Camco Inc.*, [2000] 2 S.C.R. 1067:

> ***43*** *The first step in a patent suit is therefore to construe the claims. Claims construction is antecedent to consideration of both validity and infringement issues.*
>
> …
>
> ***45*** *The key to purposive construction is therefore the identification by the court, with the assistance of the skilled reader, of the particular words or phrases in the claims that describe what the inventor considered to be the "essential" elements of his invention.*

[28] The relevant date for construction of the ’191 patent, being a “new” *Patent Act* patent, is the date of its publication, October 2, 1997. Construction is to be undertaken by the Court, viewing the claims as of that date through the eyes of a person skilled in the art, assisted if needed by expert evidence as to the meaning of special terms and the knowledge that such a person would bring to bear. Regard is to be given to the whole of the disclosure of the patent and the claims. Again, there are many authorities stating such propositions. One is the Federal Court of Appeal, Sharlow JA. in *Novopharm Ltd. v. Janssen-Ortho Inc.*, 2007 FCA 217 at paragraph 4. (It is to be noted that the patent there was an old Act patent therefore the date for consideration was different.):

> ***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.*

PERSON SKILLED IN THE ART

[29] The parties spent little time in argument defining the person or persons who represented those skilled in the art to whom the '191 patent was addressed. Novopharm, through its witness Dr. Kanfer at paragraph 18 of his affidavit stated that such a person was:

> *"…a person with a degree in science, focused on the physical sciences and preferably in the field of pharmacy, with at least several years experience in pharmaceutical formulation in an academic or industry setting."*

[30] Applicant's counsel in oral argument accepted that definition. I accept it as well.

THE '191 PATENT-DESCRIPTION

[31] The '191 patent begins at page 1 in stating that the invention is directed to a particle size range of a class of pharmaceutical compounds known as benzothiophenes, which size range enhances bioavailability and allows control during manufacturing:

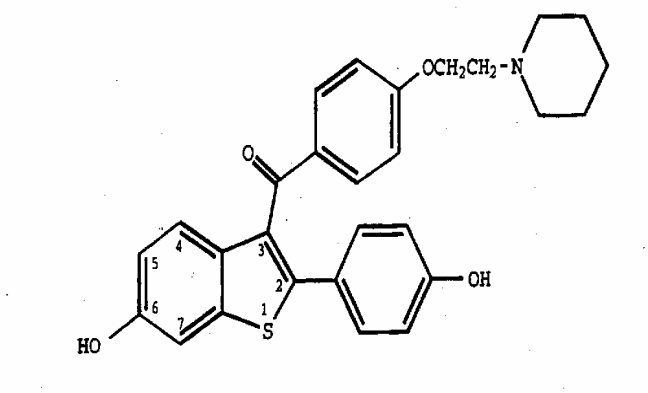
> *This invention relates to the fields of pharmaceutical and organic chemistry and provides a benzothiophene compound, in particulate form, which is useful for the treatment of various medical indications, including osteoporosis and lipid lowering. More particularly, the benzothiophene is of a particle size range which allows enhanced bioavailability and control during the manufacturing process.*

[32] Later on page 1 and over to page 2, the patent restricts the discussion to one benzothiophene, raloxifene, useful in treating osteoporosis, but states that raloxifene has solubility problems that affect both its bioavailability and manufacturing:

> *The advancement of raloxifene has been somewhat hampered by its physical characteristics, both as to bioavailability and in manufacturing. For example, it is generally insoluble, and this can adversely affect the bioavailability. Clearly, any improvement in the physical characteristics of raloxifene, would potentially offer a more beneficial therapy and enhanced manufacturing capability.*

[33] At page 2 a general description of the invention of the patent is given. Raloxifene is depicted in its chemical diagrammatic form:

> *This invention provides a compound of formula I*



> *and pharmaceutically acceptable salts and solvates thereof, characterized in that the compound in its particulate form, said particles having a mean particle size of less than about 25 microns, and preferably between about 5 and about 20 microns.*

[34] Thus the invention is stated to be the provision of raloxifene in particulate size less than about 25 microns and preferably between about 5 and about 20 microns. Further statements are made as to at least 90% of the particles being less than 50 microns, preferably less than 35 microns.

It is pointed out that this raloxifene can be formulated with pharmaceutical compounds for treatment of osteoporosis and other conditions.

[35] The benefits of bringing the particle sizes within the specified narrow range are said to be in respect of dissolution, bioavailability and improved manufacturing capabilities. At pages 2 and 3 the patent says:

> *It has now been found that by processing compounds of formula I, to bring their particle sizes within a specified narrow range, pharmaceutical compositions may be prepared which exhibit for their active ingredient both a consistent in vitro dissolution profile and in vivo bioavailability. In addition to bringing about these desired dissolution/bioavailability characteristics, the control of particle size to narrow range has also resulted in significant improvements in manufacturing capabilities.*

[36] The particle size and range is again set out at page 3:

> *The mean particle size of compounds of formula I, as set out by the invention, is less than about 25 microns, preferably between about 5 and about 20 microns. Further, the invention encompasses formula I compounds with at least 90% of the particles having a particle size of less than about 50 microns, preferably less than about 35 microns. More preferably, the mean particle size range is between about 5 and about 20 microns, with at least 90% of the particles having a size of less than about 35 microns.*

[37] Pages 4 and 5 of the patent discuss conventional wisdom, that poor solubility can be improved by reducing particle size but reduced particle size gives rise to manufacturing problems such as heating of the ingredients and caking in the machinery. There must be a compromise between the two:

> *Often, compounds which have poor solubility profiles can have their bioavailability enhanced by increasing the surface area of the formulated particles. The surface area generally increases per unit volume as the particle size decreases. Various techniques for grinding or milling a drug substance are well known in the art…very finely divided material presents difficulties and cost in capsule filling or tablet preparation, because the material will not flow, but becomes caked in finishing machinery. Such finishing difficulties generate non-homogeneity in the final product, which is not acceptable for a drug substance. Additionally, the milling process physically generates heat and pressure on the material, such conditions lead to chemical degradation of the compound, thus such milling techniques are usually kept to a minimum.*
>
> *Therefore, there is always dynamic between the properties which yield the maximum bioavailability (particle surface area) are the practical limits of manufacture. The point of compromise which marks this "best solution" is unique to each situation and unique as to its determination.*

[38] At page 5 the patent tells the reader that, in the raw state, raloxifene has a broad size distribution with a volume diameter of about 110-200 microns. That size is measured by a Horiba LA900 device. At page 7 the particle size measurement technique is more fully described in respect of raloxifene whose particle size has been reduced:

> *The particle size of the reduced raloxifene HCl was measured as follows. The laser scattering particle sizes distribution analysis was effected on a small sample of the reduced material which is suspended in approximately 180 ml of dispersant solution. Sample is added to the dispersant until an acceptable level of laser light obscuration achieved at which point the particle sizes distribution is measured. Prior to the sample suspension the dispersant solution was prepared by adding 20 drops of Coulter 1A dispersant to a saturated aqueous solution of raloxifene HCl. The dispersant solution was filtered through a 0.2 micron microporous membrane filter to provide the necessary particle-free suspending dispersant.*
>
> *Within five minutes of the preparation of the dispersion, triplicate particle size measurements were performed.*

[39] At page 8 there begins a discussion as to the rate of dissolution of raloxifene and its absorption into the gastrointestinal tract, thus the effect upon bioavailability:

> *Given the low solubility, the rate at which the dosage form dissolves in the gastrointestinal tract can potentially impact the rate and extent of absorption of the active compound. Two related physical properties of the bulk drug which can alter the dissolution rate of the dosage form are particle size and surface area.*

[40] There follows at pages 9 to 12 a description of *in vitro* and *in vivo* testing of raloxifene of various particle sizes obtained through recrystallization (said to be a control batch), micronizing and two forms of milling. As stated at page 9:

> *To ascertain the effect of particle size/surface area of raloxifene HCl on in vitro dissolution, lots with varying particle size distribution were obtained via recrystallization and further modified through various milling technologies.*

[41] Tables showing the surface area and particle size and rate of dissolution of the samples are provided as Tabs 1, 2 and 3. At page 11, the patent postulates that the surface area of the particles as measured by a certain technique does not predict its dissolution:

> *It is postulated that the surface area as measured by nitrogen adsorption for the various types of milled raloxifene does not predict the effective surface area accessible to the dissolution medium.*

[42] At page 12 the patent states that, as a result, a decision was made to pursue particle size as a parameter for drug performance:

> *Based upon these findings, the decision was made to pursue particle size distribution as a control parameter to ensure consistent*

> *performance of the drug product with regards to release of the drug component.*

[43] A study was conducted, as set out in pages 12 to 15 of the patent, where it states that monkeys were fed from two batches of raloxifene, one with a mean particle size of 48.1 microns (Lot 5A) and one with a mean particle size of 9.0 microns (Lot 5B).

[44] At page 15 the patent states that particle size is critical and that the study confirms that *in vitro* testing can confirm the *in vivo* absorption:

> *This data is further evidence of the critical nature of the particle sizes distribution on its impact on bioavailability. The study also confirms the discriminating ability of the in vitro dissolution method and its relationship to in vivo absorption. Once again, the differences observed in the in vitro dissolution profiles translated into in vivo absorption differences.*

[45] Based on this work, certain particle size specifications were established and work was undertaken to justify the range established. At page 15 and at page 17 the reader was told that bulk lots of raloxifene were milled and formulated into tablets which were then studied:

> *Based upon the above work and physical property data generated, a particle size specification was established. The invention provides that the mean particle sizes, as determined by laser light diffraction, should be less than about 25 microns. In addition, 90% of the particles by volume should be under 50 microns, which allows for characterization of the distribution. Preferably, the size between about 5 and about 20 microns, and 90% of the particles have a size of less than about 35 microns. To justify this range, bulk lots were produced by pin milling and samples of the available extremes were manufactures into formulated tablets and in vitro dissolution testing. In one study, six bulk lots of raloxifene hydrochloride (ca. 1 kg) were received and manufactured into formulated 60 mg raloxifene HCl*

> *tablets representative of the tablets being utilized in Phase III clinical testing.*
>
> …
>
> *Another similar study was performed with 7 different particle size distribution of bulk drug, with each again being formulated into 60 mg tablets.*

[46] Data respecting these studies is presented, including tables. A conclusion is set out at page 18. This conclusion, the Applicant argues, is the inventive step of the patent: namely, that within the stated particle size range, the *in vivo* absorption/bioavailability characteristics are surprisingly consistent:

> *Given the relationship shown between in vitro dissolution and in vivo absorption, it follows that the particle size distribution range claimed in this patent will provide surprisingly consistent in vivo absorption/bioavailability characteristics.*

[47] There follows at pages 18 and 19 a discussion as to particle sizes and manufacturing. Too fine a particle size results in poor flow and poor control of the process. Thus the particle size constraints of the patent result in more amenable processing. At page 19:

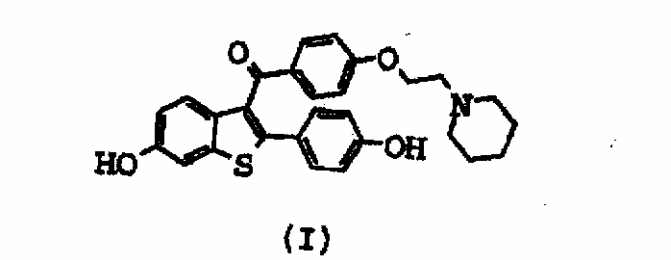
> *Too fine a granulation distribution can lead to poor granulation flow and poor control of individual table weight during the compression step. Thus the narrow particle size constraints previously mentioned have also resulted in making the process more amenable to automation by reducing the variations in water required during the granulation step and producing dry milled granules of the appropriate distribution to prevent the rejection of tablets during compression due to unacceptable tablet weight.*

[48] From page 19 to page 36 various formulas for manufacturing tablets containing raloxifene are provided together with the added ingredients (excipients). The patent ends with 8 claims.

THE CLAIMS OF THE ’191 PATENT

[49] The 8 claims of the ’191 patent are as follows:

1. A compound of formula I



(I)

and pharmaceutically acceptable salts thereof, characterized in that the compound is in particulate form, said particles having a mean particle size of less than 25 microns, at least 90% of said particles have a size of less than 50 microns.

2. The compound of claim 1 wherein said particles have a mean particle size of between 5 and 20 microns.

3. The compound of claim 1 or 2 wherein at least 90% of said particles have a size of less than 35 microns.

4. A pharmaceutical composition comprising or formulated using a compound according to any one of claim 1, 2 or 3, or a pharmaceutically acceptable salt thereof, in combination with one or more pharmaceutically acceptable carrier, diluent or excipient.

5. A compound of any one of claim 1, 2 or 3 which is non-solvated crystalline 6-hydroxy-2- (4-hydroxy-phenyl) -3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene hydrochloride.

6. The use of a compound of claim 5 or a pharmaceutically acceptable salt thereof for inhibiting osteoporosis in a person in need thereof.

7. The use of a compound of claim 5 or a pharmaceutically

> *acceptable salt thereof for preventing breast cancer in a woman in need thereof.*
>
> *8. A pharmaceutical composition comprising or formulated using the compound of claim 5 and one or more pharmaceutically acceptable carrier, diluent or excipient.*

[50] The compound as depicted in Formula I of claim 1 is the same as that as written in claim 5 and can be simply stated as raloxifene. The pharmaceutically acceptable salt can be described for the purposes of this proceeding as hydrochloride. Thus the claims can be more briefly be rewritten as:

a. Raloxifene hydrochloride in particulate form having a mean particle size of less than 25 microns, at least 90% of which particles have a size less than 50 microns.
b. As per claim 1 with a mean particle size of between 5 and 20 microns.
c. As per claims 1 and 2 in which 90% of the particle size is less than 35 microns.
d. A pharmaceutical composition using the compound of any of claims 1, 2 or 3.
e. A compound of any of claims 1, 2 or 3 comprising raloxifene hydrochloride.
f. Use of the claim 5 compound to inhibit osteoporosis.
g. (Not at issue). Use of the compound in preventing breast cancer.
h. A pharmaceutical composition of claim 5.

[51] The parties are agreed as to the essential elements of the claims and that for purposes of these proceedings, we need only to look at claims 1, 2 and 3. The essential elements of those claims are:

Claim 1: -Raloxifene hydrochloride

i. in particulate form

ii. such particles having a mean particle size of less than 25 microns, at least 90% of which particles have a size of less than 50 microns

Claim 2: The compound of claim 1 where the mean particle size is between 5 and 20 microns.

Claim 3: The compound of claim 1 and 2 wherein at least 90% of the particles have a size of less than 35 microns.

INFRINGEMENT

[52] It is agreed that, for purposes of considering Novopharm's allegations as to non-infringement, only claim 1 needs to be considered. It is assumed that Novopharm will be formulating its raloxifene hydrochloride into pharmaceutical compositions for use directed to osteoporosis. The only issue is as to the particle size of the raloxifene hydrochloride. The broadest parameters for particle size are those found in claim 1 which requires the particle size to be less than about 25 microns, and at least 90% of the particles to have a size of less than 50 microns.

[53] Novopharm's Notice of Allegations at pages 36 and 37 addresses its non-infringement allegation and states, *inter alia*:

> *Novopharm's Tablets will not infringe any of the claims of the '191 Patent. Novopharm's Tablets will not contain raloxifene or a pharmaceutically acceptable salt thereof with a particle sizes of less than about 25 microns, and at least 90% of the particles having a size of less than 50 microns, as claimed and required in the '191 Patent. The particles of raloxifene that Novopharm will use and incorporate into its Novopharm Tablets will have a mean particle size significantly greater than 25 microns, and the raloxifene (or a*

> *pharmaceutically acceptable salt thereof) particles used by Novopharm will not have at least 90% of the particles with a sizes of less than 50 microns.*

[54] Novopharm relies on two things in support of its allegation. First, the information that it supplied to Health Canada in support of its own Abbrieviated New Drug Submission (ANDS). Second it relied on testing conducted by an outside laboratory known as Dalton and its employee Ms. Zhao who provided an affidavit and was cross-examined. Comments were provided thereon by Novopharm's expert Dr. Biggs.

[55] The Applicant relied on testing of samples provided by Teva, an organization related to Novopharm, in the context of certain United States litigation. It was agreed by the parties that the results of such testing may be introduced into this proceeding as if the samples had been provided by Novopharm in the context of these proceedings. The testing was conducted by an outside laboratory, PTL, under the supervision of Ms. Ganden, who provided an affidavit and was cross-examined in these proceedings. The Applicant's expert, Dr. Bugay, commented on this testing and the results.

[56] Each of Drs. Biggs and Bugay also provided comments as to the testing done by the other parties and conclusions that might be drawn as to the evidence of each other.

[57] I have no reason to doubt that all of the testing was performed as reported and that the results were accurately reported. I also have no reason to be critical of the evidence given by any of Ganden, Zhao, Biggs or Bugay or their independence or credibility.

[58] The critical issue is directed to how the particle size of the raloxifene is measured. I accept the evidence of Dr. Bugay in cross-examination found at pages 40 to 42 of the transcript, pages 1569 to 1570 of the Record, that in measuring particle size one must be careful not to cause the particles to dissolve, to be sure that the particles are not agglomerated, and to ensure that particles are not fractured during the course of measurement. I also accept the evidence of Zhao at paragraph 6 of her affidavit that bubbles in the sample may cause problems with measurement.

[59] The information given in the '191 patent as to how measurements of particle size were made is set out at pages 5 and 7:

> *The efficiency of the milling is checked by sampling using a Horiba LA900 Laser Scattering Particle Size Distribution Analyzer and the final particle size is checked in a similar manner.*
>
> …
>
> *The particle size of the reduced raloxifene HCl was measured as follows. The laser scattering particle size distribution analysis was effected on a small sample of the reduced material which is suspended in approximately 180 ml of dispersant solution. Sample is added to the dispersant until an acceptable level of laser light obscuration achieved at which point the particle size distribution is measured. Prior to the sample suspension the dispersant solution was prepared by adding 20 drops of Coulter 1A dispersant to a saturated aqueous solution of raloxifene HCl. The dispersant solution was filtered through a 0.2 micron microporous membrane filter to provide the necessary particle-free suspending dispersant.*
>
> *Within five minutes of the preparation of the dispersion, triplicate particle size measurements were performed. Triplicate measurements are effected as a minimum check a) to produce more reliable measurements and b) to check the equivalent sampling of the*

> *suspended material has been reproducible i.e., the suspension has not settled.*
>
> *The results were automatically recorded and displayed graphically to give a frequency percentage vs. undersize and a cumulative percentage vs. undersize characteristics curves for the sample.*

[60] It appears that in the testing provided to the Court a device known as a Malvern Mastersizer was used rather than a Horiba LA900 but Counsel for the parties were agreed that these devices may be considered as equivalent for the purposes of this proceeding.

[61] Two matters should be noted in respect of the procedure for particle size measurement set out in the ’191 patent. First, a dispersant identified as Coulter 1A was used. Second, the procedure is silent as to agglomeration and if any were noticed, how, if at all, it is to be dealt with. It is noted that measurements are taken within five minutes of treating the sample with the dispersant.

[62] I accept the evidence of the Applicant’s expert Dr. Bugay as to the manner in which a sample would be prepared and handled as set out in paragraph 27 of his affidavit:

> *27. It is important to note that all particle size measurements are designed to measure representative samples of the individual fine particles of the material of interest as opposed to clumps of those particles such as aggregates or agglomerates. Consequently, regardless of the measuring apparatus used, the accuracy of a particle size measurement is highly dependent on ensuring that the measured material is in fine particles and not clumps. This is achieved through proper sample preparation and handling which include: (1) de-aggregating the original sample such that the individual fine particles are being measured; (2) selecting the medium to suspend the individual particles within for the subsequent measurement; (3) utilizing a dispersing agent to prevent aggregation; and (4) concentrating the particles within the suspension matrix in order to achieve the proper obscuration.*

[63] I accept, and no party challenged, that this procedure would have been one known to and followed by the relevant person skilled in the art as of the date of publication of the ’191 patent application, October 2, 1997.

[64] Turning then to Novopharm’s submissions as to the evidence of non-infringement. First Novopharm relies on its submission to Health Canada in support of its Abbreviated New Drug Submission found as Exhibit D to the affidavit of Dr. Bugay. Data is given in respect of two pilot batches of its raloxifene hydrochloride. Particle size measurements on a Malvern Mastersizer were given as having a mean particle size for one batch as 37.4 microns and the other as 39.4 microns which is well above the value of 25 microns given in claim 1. A 90% particle size value for the first batch is given as 92.0 microns and the second as 97.2 microns, again well above the value of 50 microns establishes in claim 1. Novopharm argues that its submissions to Health Canada must be taken very seriously and any deviation from such values may well result in serious consequences. I agree that, if there were no other evidence, then such evidence as found in the submission may possibly be taken as determinative. Here, however, there is other evidence, all of which must be evaluated.

[65] The method by which these samples were measured is set out at Exhibit B of the Dr. Biggs affidavit, pages 607 and 608 of the Record and commented upon by him at paragraphs 50 to 52 of his affidavit. There are two matters of note. First the dispersant used was isopropyl alcohol (IPA) not the Coulter 1A of the patent. Second, the sample was subjected to vortex mixing for 30 seconds

(described in the evidence as attaching a suction cup to the vessel containing the sample and shaking it) and to sonification for five seconds (described in the evidence as the application of ultrasonic energy waves to the sample). It must be remembered that the patent is silent as to how, if at all, the sample is mixed or shaken or whether sonification is used.

[66] The Applicant criticized this method (called the Teva method) on two grounds. The first is the use of IPA as the dispersant and not Coulter 1A. The second ground was that there was insufficient shaking or mixing of the sample so as to get rid of agglomeration.

[67] Novopharm ran another set of tests, this time through an independent laboratory known as Dalton, by one of its employees Ms. Zhao. Zhao's affidavit testifies that two sets of tests were run in accordance with a protocol provided by a lawyer in the firm acting for Novopharm. The first tests were suspected of being influenced by the presence of bubbles so a second set of tests was run. At the hearing, relying on questioning of Dr. Biggs found at page 44 of the transcript of his cross-examination (page 1788 of the Record), Applicants counsel argued that the lawyer devised the protocol. I am satisfied in reading the questions and answers that while the lawyer wrote the protocol, the protocol was devised by Dr. Biggs, not the lawyer. The protocol is said to follow that set out in the '191 patent to the extent that it can be done.

[68] Coulter 1A is used as a dispersant (not IPA). The sample was shaken by hand briefly. The Applicants Counsel argues that this was insufficient to get rid of agglomeration. Ms. Zhao was clear in her cross-examination that sonification would not be recommended for particle size

analysis. She said in answer to questions 186 to 192 as to sonification that it is not recommended for particle size analysis:

> *186. Q. So when we talked about the short mixing, that was the hand-mixing that we were talking about?*
> *A. Yes*
>
> *187. Q. And it says: "...No sonification should be used…"*
> *A. Yes.*
>
> *188. Q. What is sonification used for?*
> *A. The sonification, you are asking what is sonification used, right?*
>
> *189. Q. Yes.*
> *A. The sonification when we use in general lab…in general term, in lab, we use the gassing purpose, for the dissolving purpose.*
>
> *190. Q. For dissolving purpose?*
> *A. Yes. You put your solid in there and then you have your solution in there but some time you want to de-gas because there is some gas in there, you put in sonification…and then start it. That's the sonification works.*
>
> *191. Q. So sonification can get rid of gas that is in the solution?*
> *A. Yes. That's the sonification works for.*
>
> *192. Q. can it also be used for agglomerates if a particle is agglomerated?*
> *A. We use for in the lab, we use this for dissolving purpose. Some sample takes time dissolve, that helps dissolve. But this…in particle sizes, sonification is not recommended.*
>
> *193. Q. It is not recommended?*
> *A. No. It is for general lab purpose but not for particle size analysis.*

[69] The second set of tests run by Zhao shows that in the two samples tested the mean particle size were 43.7 microns and 40.4 microns, well above the 25 microns of Claim 1 and the 90%

criterion was 108.0 microns and 100.3 microns, again well above the 50 micron requirement of claim 1 (see Exhibit B to Zhao, page 556 of the Record). The first test (Exhibit A to Zhao, page 548) gave results equally above the limits of claim 1.

[70] The Applicant relies on testing conducted by PTL, supervised by Ms. Ganden. PTL in 2004 had, at the request of Mark Feldstein, a lawyer in the United States law firm of Finnegan Henderson, prepared a protocol for the testing of raloxifene hydrochloride particle sizes. This protocol (found as Exhibit H to the affidavit of Feldstein, pages 80 to 93 of the Record) was submitted by Lilly US to the United States Food and Drug Authority as part of its submissions as to its raloxifene hydrochloride drug. In this regard it is on a footing similar to Novopharm's ANDS submission. At page 80 of the Record, first page of the submission, it is stated that three dispersants were investigated, hexane, isopropyl alcohol (IPA) and water, and that in water containing 20 drops per litre of Coulter 1A the particles dispersed rapidly. The others, hexane and IPA, caused particles to clump together and form agglomerates. It is not stated whether sonification was used. Stir rates and agitation rates are mentioned.

[71] In 2006 PTL, at the request of Feldstein, conducted particle size analysis on the two Teva samples agreed to be relevant in respect of the Novopharm product at issue here. A report was provided, Exhibit A to the Ganden affidavit, Exhibit F to the Feldstein affidavit, pages 65 to 78D of the Record. The results of the testing of the two samples appear at page 67 of the Record. The mean particle size of the first sample was 25.18 microns, very near the 25 micron limit of claim 1 and of the second sample was 21.71 microns, within the 25 micron limit of claim 1. The 90% figure

for the first sample was 56.55 microns thus it was above the 50 microns limit of claim 1 and for the second sample was 45.27 microns thus within the 50 micron limit of claim 1. In sum, the first sample was outside the two parameters of claim 1, the second sample was within.

[72] It appears that the protocol used by PTL in its testing is that which it developed in 2004. Although not entirely clear from that protocol, it appears, for instance as set out in paragraph 5 of the Reply affidavit of Dr. Bugay, pages 147-148 of the Record that, after the dispersant was added to the sample, the sample was subjected to hand shaking followed by at least 15 seconds of sonification. At paragraph 6 and 7 of the same affidavit at page 148 of the Record, Dr. Bugay refers to a chart, found at page 1490 of the Record, showing particle size measured as against ultrasonification time showing a visible reduction in particle size over the first fifteen seconds, a relatively stable period, then a more gradual drop after three minutes.

[73] Drs. Bugay and Biggs have a clear difference of views as to the effect of sonification. Dr. Bugay says that sonification for fifteen seconds serves merely to break down agglomeration. Dr. Biggs says that sonification would not be used at all unless agglomeration was visually detected, and that any sonification would result in some fracture of some particles thus reducing the overall particle size of the entire sample. The exchanges of views are best set out in their second affidavits. The differences between them cannot be resolved on the basis of credibility, I have not seen the witnesses, I have only affidavits and transcripts. No exchange in cross-examination is so striking as to enable a credibility assessment to be made. Thus, they both are credible.

[74] We are left with this. Novopharm has in its ANDS told Health Canada that its particle size will be outside the range claimed in the ’191 patent. However this data appears to have been created by testing using a dispersant (IPA) that Lilly told the United States Authorities, would lead to agglomeration, therefore readings according to Lilly that are too high. Novopharm therefore had an independent lab test its material using the dispersant called for in the patent, Coulter 1A. The tests again showed both samples outside the range claimed in the patent. Lilly criticised this second test for not shaking the sample sufficiently including applying it to sonification so as to ensure there was no agglomeration.

[75] Lilly ran its own tests on two samples. One was found to be inside the claimed range, one outside. Lilly used the dispersant described in the ’191 patent and subjected the sample to shaking for one minute followed by fifteen seconds of sonification.

[76] The patent is silent as to shaking or sonification or any other such manipulation of the material to be tested.

[77] I take note of what Ms. Zhao of Dalton said as to the testing that she did on behalf of Novopharm. She said that did she not observe any agglomeration of the sample to be tested. In the exchange set out in earlier in these Reasons it is to be noted that she said that for testing of particle size sonification is not normally used.

[78] The point of shaking or sonification is to ensure that there is no agglomeration. The evidence satisfies me that, as of the publication date of the patent application, October 1997, a person skilled in the art in measuring particle size would want to get rid of agglomeration and that if any agglomeration was detected it would be by visual inspection and that shaking would be the usual remedy. I am satisfied, particularly having regard to the Affidavit Reply Affidavit of Dr. Biggs, that sonification creates substantial energy in the sample and that some fracture, that is, reduction in size of some particles, is likely to occur.

[79] The patent is silent as to de-agglomeration techniques, if needed. I agree with the opinion expressed by Dr. Biggs at paragraph 63 of his first Affidavit, pages 601 and 602 of the record, that if agglomeration were a problem requiring the application of techniques in applying energy such as sonification, then the patent would have said so.

[80] What is to be determined is the measurement of particle size as it would have been understood and done as of October, 1997. The Dalton technique more nearly resembles what would have been understood at that time. The Dalton technique results in both samples tested being measured as clearly outside the parameters of claim 1 of the ’191 patent. The more aggressive PTL technique utilizing energy supplied by sonification results in only one of two samples being within those parameters. Therefore, I find, on a balance of probabilities, that Novopharm’s allegation of non-infringement, is justified.

VALIDITY - GENERALLY

[81] Novopharm has attacked the validity of the ’191 patent claims on two grounds, obviousness and utility.

[82] As a first step, the claims have already been construed. The essential elements of claim 1 are:

Raloxifene hydrochloride

i. in particulate form

ii. such particles having a mean particle size of less than 25 microns at least 90% of which are less than 50 microns.

of claim 2 are:

- The compound of claim 1 where the mean particle sizes is between 5 and 20 microns.

of claim 3:

iii. The compound of claim 1 and claim 2 wherein at least 90% of the particles have a size of less than 35 microns.

[83] The balance of the claims are directed to compounds and pharmaceutical compositions and uses. Counsel have agreed that it is unnecessary to consider them here, for if any of claims 1, 2 or 3 are valid, so are claims 4 to 8; conversely if claims 1, 2 and 3 are invalid, so are claims 4 to 8; if one or more only of claims 1, 2 or 3 are valid, then to the extent that claims 4 to 8 depend on a valid claim, they too are valid.

[84] The ’191 patent acknowledges at pages 1 and 2 previously set out in these reasons that raloxifene hydrochloride was a known compound useful in treating osteoporosis and other health conditions, but that it was generally insoluble and that can affect bioavailability. At page 5 of the ’191 patent we are told that “raw” raloxifene hydrochloride comprises particles with a volume diameter of about 110-200 microns and a broad size distribution.

[85] At pages 4 and 5 of the ’191 patent it is acknowledged that it is known that often compounds with poor solubility can have bioavailability enhanced by decreasing particle size. However, we are told that it was known in the prior art that a reduction of particle size brings with it associated problems presented by manufacturing difficulties such as overheating and caking in the machinery. The experts put forward by the parties, Williams for the Applicants at paragraph 25 to 28 of his affidavit and pages 37 to 42 of the transcript of his cross-examination, and Kanfer for Novopharm at paragraph 53 to 67 of his affidavit and questions 16 to 48 of the transcript of his cross-examination, both agreed.

[86] The ’191 patent states the problem at page 5 which is to find the “best solution” for the particular drug in question:

> *Therefore, there is always dynamic between the properties which yield the maximum bioavailability (particle surface area) and the practical limits of manufacture. The point of compromise which marks the “best solution” is unique to each situation and unique as to its determination.*

[87] Dr. Williams in paragraph 28 of his affidavit states that each pharmaceutical ingredient is different. Consequently a pharmaceutical scientist must determine what particular factors to focus

upon and design experiments and analyse their effects before arriving at a best solution. Dr. Kanfer at paragraphs 63 to 68 of his affidavit appears to agree with this proposition but states that such an assessment was part of the standard approach in the production of pilot plant batches. In answering Question 35 on cross-examination Dr. Kanfer said:

> *35. Q. Okay, and for a person skilled in the art, the choice and design and interpretation of this is complex. You have to weigh the factors, see what the effect of them is to try and get to your ultimate objective?*
>
> *A. As I mentioned, that is the area which is known biopharmaceutics, which in the pharmaceutical course an undergraduate student would be well aware of these kind of things.*

[88] Dr. Williams, in the course of his cross-examination, particularly at pages 38 to 43 agrees that it was known that bioavailability is improved by increasing the surface area of particles and that manufacturing capability would decrease as a result.

[89] To this point therefore, there is nothing disclosed by the patent that would not have been known to a person skilled in the art as to the problem and how to address it and that any person skilled in the art could resolve the problems routinely to arrive at a "best solution". Nothing so far is unobvious, nor is any further disclosure needed to show utility.

[90] The '191 patent at page 3 states a particle size and range. As previously discussed, this is the expected result that would be achieved by a person skilled in the art, even an undergraduate:

> *The mean particle size of the compounds of formula I, as set out by the invention, is less than about 25 microns, preferably between 5 and about 20 microns. Further, the invention encompasses formula I*

> *compounds with at least 90% of the particles having a particle size of less than about 50 microns, preferably less than about 35 microns. More preferably, the mean particle size range is between about 5 and about 20 microns, with at least 90% of the particles having a size of less than about 35 microns.*

[91] The ’191 patent describes a number of tests conducted which, the Applicant states, led to a surprising conclusion, namely, that within the range determined for particle size there is surprisingly consistent *in vivo* absorption/bioavailability characteristics. At page 18 the ’191 patent says:

> *As with the previous set of particle size distribution, the comparable dissolution profiles obtained with these particle size distributions support the range of particle size given in this invention. Given the relationship shown between in vitro dissolution and in vivo absorption, it follows that the particle size distribution range claimed in this patent will provide surprisingly consistent in vivo absorption/bioavailability characteristics.*

[92] In other words, the Applicant is saying that while the optimization of the range of particle size may have been routine work within the skill of a person skilled in the art, it lead to surprising results, namely that, within that range the *in vivo* absorption/bioavailability characteristics of the raloxifene hydrochloride was surprisingly consistent. Thus, within the range, large particles or small, the *in vivo* absorption/bioavailability of the compound would be about the same. That, says the Applicant, is the inventive concept.

[93] Novopharm attacks the validity of the claims on two basis:

1. Obviousness – that is, a person skilled in the art would have known to optimize particle size range

2. Utility – if one says that the inventive concept is that within the particle size range there is surprising *in vivo* absorption/bioavailability consistency, then one has not demonstrated that by the data provided in the patent nor could this have been soundly predicted as of October 1997 based on the data which is presented.

[94] These arguments are interrelated. I will turn first to the obviousness.

OBVIOUSNESS

[95] The Supreme Court of Canada has recently, in *Apotex Inc. v. Sanofi-Synthelabo Canada Inc.*, 2008 SCC 61 provided a review and restatement of the law as to obviousness in Canada. The Federal Court of Appeal carried the matter further in *Apotex Inc. v. Pfizer Canada Inv.*, 2009 FCA 8. In *Sanofi* Rothstein J. for the Court endorsed the English "restated" *Windsurfing* test as a proper approach to obviousness. At paragraph 67 he 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.]*
>
> *It will be at the fourth step of the Windsurfing/Pozzoli approach to obviousness that the issue of "obvious to try" will arise.*

[96] If we look at the ’191 patent with the aid of these criteria it can be seen that while optimization of particle size range would have been a known task, which could be accomplished routinely by a person skilled in the art, the result, as stated in the patent, as being consistent *in vivo* absorption/bioavailability characteristics, was according to the patent, surprising.

[97] There is ample law to support the proposition that new compositions that could be arrived at by a person skilled in the art are not in themselves inventive. However if they are found to possess unexpected utility, then they could be elevated to the status of an invention. I quote from Thurlow J. (as he then was) in *Société des Usines Chimiques Rhone-Poulenc v. Jules R. Gilbert Ltd.* (1968), 55 C.P.R. 207 (ExQ), aff’d [1968] S.C.R. 950, at page 227:

> *The invention as claimed in claim 18 is one for a process which includes the reacting of certain known chemical substances with certain other known chemical substances in a well-known type of chemical reaction for the purpose of producing a result which any skilled chemist would have expected. All this is admitted…and from*

> *it it follows, notwithstanding the further fact that no one had previously carried out the reaction using the particular starting substances, that there could have been no invention in the process unless it has been found to produce substances possessing utility which on the basis of previous knowledge could not have been expected from them. As mere new chemical substances they would not constitute inventions unless they were found to possess unexpected utility but if they were found to possess such utility, for example, as drugs or as paints or dyes, or for any practical purpose, they might both constitute inventions of new and useful substances and at the same time supply the utility necessary to elevate the well-known method as applied to the materials that would produce them to the status of an invention as well. This, as I understand, is the effect of the reasoning of Jenkins, J., in Re May & Baker Ltd. and Ciba Ltd. (1948), 65 R.P.C. 255, which was adopted and approved by the Supreme Court of Canada in Commissioner of Patents v. Ciba Ltd., 30 C.P.R. 135, 19 Fox Pat. C. 18, 18 D.L.R. (2d) 375, [1959] S.C.R. 378.*

[98] Thus, as long as the requirement of utility is satisfied, the subject matter of the claim can be said to be inventive. For this reason I must pass on to the allegation as to lack of utility.

UTILITY

[99] The *Patent Act*, section 2 in defining an "invention" requires that the invention be "new and useful". As stated by Thorson P. in *Minerals Separation North American Corp. v. Noranda Mines Ltd.* [1947] Ex.C.R. 306 at page 317, there is a requirement that the description of the patent set out all the information known to the inventor, without leaving the matter to chance, so as to enable the invention to be put into practice:

> *The description must also give all information that is necessary for successful operation or use of the invention, without leaving such result to the chance of successful experiment, and if warnings are required in order to avert failure such warnings must be given. Moreover, the inventor must act uberrima fide and give all*

> *information known to him that will enable the invention to be carried out to its best effect as contemplated by him.*

[100] It is clear that unexpected utility can support an otherwise obvious invention. However that utility must be clearly stated in the description. Merely to state that there are advantages is insufficient. I reviewed this law in *Eli Lilly Canada Inc. v. Novopharm Ltd.*, [2008] 2 F.C.R. 749 (appeal dismissed for mootness [2008] 3 F.C.R. 449, leave to appeal to Supreme Court of Canada refused) at paragraphs 135 and 136:

> ***135*** *The invention thus lies in the determination that a compound that lies within a previously disclosed class of compounds and which possesses a previously undisclosed advantage, an advantage that "cannot be predicted with any confidence," one that a person skilled in the art would not "expect to find in a large number of the previously defined class" can be the subject of a valid patent. That "advantage" was stated by the Federal Court of Appeal in Pfizer Canada Inc. v. Canada (Minister of Health), [2007] 2 F.C.R. 137, at paragraph 31 to include a disadvantage to be avoided:*
>
> > *To meet the statutory requirement in subsection 34(1) of the Patent Act, R.S.C., 1985, c. P-4 (old Act) that a patent be "useful", the selected species must have an advantage over the [page809] class as a whole (see Consolboard Inc. v. MacMillan Bloedel (Sask.) [Ltd.], [1981] 1 S.C.R. 504, at pages 525-526), That case broadly defined the utility required for valid patent as discussed in Halsbury's Laws of England (3rd ed.), Vol. 29, at page 59:*
> >
> > > *... it is sufficient utility to support a patent that the invention gives either a new article, or a better article or a cheaper article, or affords the public a useful choice.*
>
> *However, there are no special legal requirements regarding what particular type of advantage is required. The test for advantage is*

understood to include a disadvantage to be avoided, as is the case here (see I.G. Farbenindustrie at page 322).

136 *The advantage, however, must be stated in the specification. A patentee cannot merely state that the selected compound or group has advantages. The patentee must state clearly what the invention is, namely the specific advantages; as Maugham J. said at pages 321 and 323 of In re I.G. Farbenindustrie A.G.'s Patents (1930), 47 R.P.C. 239 (Ch. D.) case referred to by the Federal Court of Appeal in Sanofi-Synthelabo Canada Inc. v. Apotex Inc. (2006), 282 D.L.R. (4th) 179. In the matter of Farbenindustrie, Maugham J. states at pages 322 and 323:*

> *It is clear, for example, that mere verification is not invention. (See Sharpe & Dohme Inc. v. Boots Pure Drug Co. Ld., (1928) 45 R.P.C., 153.) Where the method of manufacture is laid down in the originating patent, the selection patent must not be an exact repetition of the same process coupled with a statement of the properties possessed by the selected bodies. No man can have a patent merely for ascertaining the properties of a known substance.*
>
> *...*
>
> *I must add a word on the subject of the drafting of the specification of such a patent. It should be obvious, after what I have said as to the essence of the inventive step, that it is necessary for the patentee to define in clear terms the nature of the characteristic which he alleges to be possessed by the selection for which he claims a monopoly. He has in truth disclosed no invention whatever if he merely says that the [page810] selected group possesses advantages. Apart altogether from the question of what is called sufficiency, he must disclose an invention; he fails to do this in the case of a selection for special characteristics, if he does not adequately define them. The cautions repeatedly expressed in the House of Lords as regards ambiguity have, I think, special weight in relation to selection patents. (Natural Colour etc. Ld. v. Bioschemes Ld., (1915) 32 R.P.C. 256, at p. 266;*

> *and see British Ore etc. Ld. v. Minerals Separation Ld., (1910) 27 R.P.C. 33, at p. 47.)*

[101] In what has become known as the *AZT* case, *Apotex Inc. v. Wellcome Foundation Ltd.*, [2002] 4 S.C.R. 153 the question of adequacy of disclosure in respect of utility was canvassed first by the Trial Judge and ultimately by the Supreme Court of Canada. The principles established by the Supreme Court must, therefore, be those from which guidance is obtained the Reasons and not of the Trial Judge. The Supreme Court determined that if there was not a fulsome disclosure in the patent itself from which a person skilled in the art could conclude that there was utility, the disclosure could nonetheless be considered to be adequate for that purpose if a person skilled in the art could "soundly predict" that there would be utility. Binnie J. in his Reasons for the court set out three components for sound prediction: first, a factual basis; second an articulable and sound line of reasoning; and third, proper disclosure. He said at paragraph 70:

> ***70*** *The doctrine of sound prediction has three components. Firstly, as here, there must be a factual basis for the prediction. In Monsanto and Burton Parsons, the factual basis was supplied by the tested compounds, but other factual underpinnings, depending on the nature of the invention, may suffice. Secondly, the inventor must have at the date of the patent application an articulable and "sound" line of reasoning from which the desired result can be inferred from the factual basis. In Monsanto and Burton Parsons, the line of reasoning was grounded in the known "architecture of chemical compounds" (Monsanto, at p. 1119), but other lines of reasoning, again depending on the subject matter, may be legitimate. Thirdly, there must be proper disclosure. Normally, it is sufficient if the specification provides a full, clear and exact description of the nature of the invention and the manner in which it can be practised: H. G. Fox, The Canadian Law and Practice Relating to Letters Patent for Inventions (4th ed. 1969), at p. 167. It is generally not necessary for an inventor to provide a theory of why the invention works. Practical readers merely want to know that it does work and how to work it. In this sort of case, however, the sound prediction is to some extent the quid pro quo the*

> *applicant offers in exchange for the patent monopoly. Precise disclosure requirements in this regard do not arise for decision in this case because both the underlying facts (the test data) and the line of reasoning (the chain terminator effect) were in fact disclosed, and disclosure in this respect did not become an issue between the parties. I therefore say no more about it.*

[102] What then is the disclosure for utility in the ’191 patent which is said to support the claimed monopoly to particle sizes? Is that disclosure sufficient in itself to support the claim to utility and, if not, is there enough set out in the description in the patent so as to enable a sound prediction that all that which is claimed as to particle size will have the utility?

[103] I return to page 18 of the ’191 patent which asserts surprising consistency within the “particle size distribution range”. Looking at the claims, only claim 2 addresses a range of sizes, between 5 and 20 microns. Claims 1 and 3 only address the maximum size, a mean particle size of less than 25 microns, at least 90% of which are less than 50 (in claim 3-35) microns. Novopharm did not allege or argue ambiguity. I will proceed on the basis that a person skilled in the art would read claims 1 and 3 as defining a range with reference to what is called a “Gaussian distribution” as illustrated by Dr. Bugay at paragraph 20 of his affidavit:

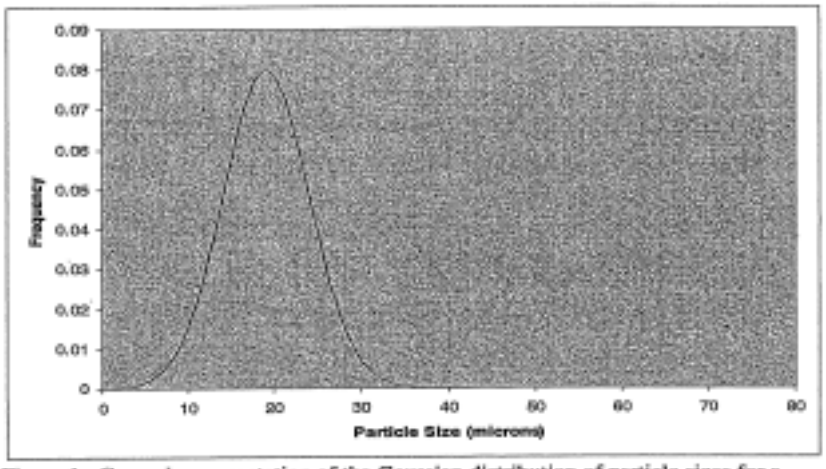


Figure 1. General representation of the Gaussian distribution of particle sizes for a pharmaceutical sample as measured by laser scattering.

[104] Thus the "range" of claims 1 and 3, in the absence of an allegation from Novopharm as to vagueness or ambiguity can be said to be that which is reasonably established by the Gaussian distribution.

[105] What information then is disclosed in the '191 patent to establish that within the range there is surprising consistency respecting *in vivo* absorption/bioavailability?

[106] The only pertinent data respecting *in vivo* absorption/bioavailability in the '191 patent is that set out in Tables 4 to 6 together with the discussion at pages 12 to 15. In these Tables and the discussion only two samples are investigated. One, Lot 5A, is well outside the claimed range, a mean particle size of 48.1 microns (vs. 25 microns) and 90% under 90 microns (vs. 50 microns). The other, Lot 5B is within, a mean particle sizes of 9.0 microns (vs. 25 microns) and 90% under

15.1 microns (vs. 50 microns). One, Lot 5A is well outside the range, the other, Lot 5B, is well inside.

[107] A single point cannot define a range. There is no data at or near the limits of the range nor is there provided data as to a number of points within the stated range so as to establish that in the range there is surprising consistency. A single point within the range does not demonstrate consistency throughout the range.

[108] Therefore the question becomes whether there is sufficient information provided in the ’191 patent to enable a person skilled in the art to “soundly predict” consistency within the range. Novopharm’s expert, Dr. Kanfer at paragraphs 82-95 of his affidavit, sets out that there is no basis for “sound prediction” set out in the ’191 patent. His opinions were not shaken on cross-examination. The Applicant’s expert Dr. Williams does not clearly address in his affidavit whether the patent contains sufficient description so as to enable consistency within the range to be soundly predicted. I have carefully reviewed Dr. Williams’ cross-examination transcript, particularly at pages 37 to 69 and I find that he cannot provide any basis for which a sound prediction could be made; instead it appears to be unsure and perhaps even confused in respect of this matter.

[109] As a result, I find that the claims 1, 2 and 3, hence 4 to 8 also in the ’191 patent are invalid in that the description contained in the patent fails to establish that the claimed particle size range has the promised utility, namely consistent *in vivo* absorption/bioavailability. Novopharm’s allegation as to invalidity for lack of utility is justified.

IN SUMMARY

[110] In summary, I have found that, on a balance of probabilities, Novopharm's allegation as to non-infringement is justified. I have further found that Novopharm's allegation as to invalidity of the claims of the '191 patent is justified on the basis that the utility of the promised invention, *in vivo* consistency of absorption/bioavailability, within the claimed particle size range has not been described and could not have been soundly predicted based on what was described. The application is therefore dismissed with costs to Novopharm.

COSTS

[111] Novopharm is the successful party. It is entitled to its costs which may be taxed, as is usual in these cases, at the middle of Column IV.

[112] Costs for two counsel, one senior, one junior, at the hearing may be taxed. Two counsel, if present, one senior, one junior, in conducting cross-examination, may be taxed. Only one counsel, a senior, is allowed in defending a cross-examination. No costs are allowed for other lawyers, in house or out house, students, paralegals or clerical persons.

[113] As in previous cases of this kind, I remain concerned that fees allowed for experts may be excessive. Here Novopharm may tax the fees of Drs. Kanfer and Biggs and may tax the reasonable costs of the experiments conducted by Dalton that were disclosed in the Zhao affidavits. Those fees shall not be disproportionately large having regard to fees charged to the Applicant by its witnesses Drs. Williams and Bugay or in the testing conducted by PTL. I may be spoken to should a dispute

arise in this regard however I expert that counsel can resolve a quantum among themselves. Nothing is allowed for any other expert or other person who may have assisted Novopharm or its witnesses.

"Roger T. Hughes"
Judge

FEDERAL COURT

SOLICITORS OF RECORD

DOCKET:	T-1562-07
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:	Hughes, J.
DATED:	March 19, 2009

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

SOLICITORS OF RECORD:

Gowlings Lafleur Henderson LLP Barristers & Solicitors 2600-160 Elgin Street Ottawa, ON K1P 1C3 Fax: (613) 563-9869	FOR THE APPLICANT ELI LILLY CANADA INC.
Bennett Jones LLP 3400 One First Canadian Place P.O. Box 130 Toronto, ON M5X 1A4 Fax: (416) 863-1200	FOR THE RESPONDENT NOVOPHARM LIMITED

Department of Justice
Civil Litigation Section
234 Wellington Street, East Tower
Ottawa, ON K1A 0H8
Fax: (613) 954-1920

FOR THE RESPONDENT
THE MINISTER OF HEALTH