Date: 20060217

Docket: T-1350-04

Citation: 2006 FC 220

Ottawa, Ontario, February 17, 2006

PRESENT: The Honourable Mr. Justice von Finckenstein

BETWEEN:

PFIZER CANADA INC. and PFIZER LIMITED

Applicants

and

THE MINISTER OF HEALTH and RATIOPHARM INC.

Respondents

REASONS FOR ORDER AND ORDER

[1] This is an application by the Applicant, Pfizer Canada Inc. ("Pfizer"), pursuant to the *Patented Medicines (Notice of Compliance) Regulations*, SOR/93-133 (the "NOC Regulations") for an Order prohibiting the Minister of Health (the "Minister") from issuing a Notice of Compliance ("NOC") to the Respondent, Ratiopharm Inc. ("Ratiopharm"), until after the expiration of Canadian Patent 1,321,393 (the "393 Patent").

[2] This application involves the drug entitled amlodipine. It is a cardiac drug that acts as a calcium channel blocker. This enhances the blood flow to the heart and reduces blood pressure. Pfizer markets and sells amlodipine besylate under the brand NORVASC.

[3] Pfizer listed two patents on the Patent Register against NORVASC: the 393 Patent and Canadian Patent No. 1,253,865 (the "865 Patent"). The 865 Patent expires on May 8, 2006 and therefore is not the subject of these proceedings. Ratiopharm seeks the issuance of a NOC to allow it to produce a generic version of the 5 mg and 10 mg amlodipine besylate tablets after the 865 Patent expires on May 8, 2006.

[4] Pfizer commenced this application by a Notice of Application dated July 19, 2004 in response to the Notice of Allegation ("NOA") from Ratiopharm dated May 31, 2004 regarding the 393 Patent. Given section 7(1)(e) of the Regulations, judgment must be issued within 24 months of this date.

NATURE OF PROCEEDINGS

[5] The nature of these proceedings was summarized by Justice Layden-Stevenson in *Fournier Pharma Inc*. v. *Canada (Minister of Health)* (2004), 38 C.P.R. (4th) 297, 2004 FC 1718 as follows:

> 6 As noted, this proceeding is brought under the Regulations. The history and scheme of the Regulations have been delineated in various decisions of the Federal Court of Appeal and need not be repeated here. See: *Merck Frosst Canada Inc*. v. *Canada (Minister of National Health and Welfare)* (1994), 55 C.P.R. (3d) 302 (F.C.A.);... Basically, issues of non-infringement and validity between the patent holder (first person) and the person seeking a NOC from the Minister (second person) originate with a NOA, served on the first person by the second person, setting out the second person's allegations, including the legal and factual basis in support. The first person may disagree and apply to the court for an order prohibiting the Minister from issuing a NOC to the second person until after expiration of the patent. (...)
>
> 8 Section 6 proceedings are not to be likened to actions for determining validity or infringement. They are proceedings in judicial review, to be held expeditiously, whose aim is to determine whether the Minister is free to issue the requested NOC. Their scope is confined to administrative purposes:

> *Apotex Inc*. v. *Canada (Minister of National Health and Welfare)* (1997), 76 C.P.R. (3d) 1 (F.C.A.). The determination must turn on whether there are allegations by the second person sufficiently substantiated to support a conclusion for administrative purposes (the issuance of a NOC) that an applicant's patent would not be infringed if the second person's product is put on the market: *Pharmacia Inc*. v. *Canada (Minister of National Health and Welfare)* (1994), 58 C.P.R. (3d) 209 (F.C.A.).
>
> 9 By merely commencing the proceeding, the applicant obtains what is tantamount to an interlocutory injunction without having satisfied any of the criteria a court would require before enjoining issuance of a NOC: *Merck Frosst Canada Inc*. v. *Canada (Minister of National Health and Welfare)* (1998), 80 C.P.R. (3d) 368 (S.C.C.);...). The Regulations allow a court to determine summarily, on the basis of the evidence adduced, whether the allegations are justified. Section 6 proceedings are not adjudicative and cannot be treated as res judicata. The patentee is in no way deprived of all the recourses normally available to enable it to enforce its rights. If a full trial of validity or infringement issues is required, this can be obtained in the usual way by commencing an action: *Pfizer Canada Inc*. v. *Apotex Inc.* (2001), 11 C.P.R. (4th) 245 (F.C.A.);...

[6] In its NOA, Ratiopharm alleges that the 393 Patent is invalid by reason of:

a) anticipation;
b) obviousness; and
c) being an improper selection patent.

Pfizer, not unexpectedly, disputes these allegations and alleges that the NOA was insufficient.

[7] In order to decide whether to grant an order prohibiting the Minister from issuing Pfizer a NOC until after the expiration of the underlying 393 Patent, this Court must conclude that Ratiopharm's allegations are not justified, *i.e*. the Court must form the view that the 393 Patent is valid, as non-infringement was not raised as an issue in these proceedings.

[8] I propose to consider the issues in the following sequence:

a) sufficiency of NOA;
b) anticipation;
c) validity of selection patent; and
d) obviousness.

PRELIMINARY ISSUE: BURDEN OF PROOF

[9] Before dealing with the substance of the allegations, I need to say a few words about the burden of proof. This issue has been extensively canvassed by this court and the court of appeal. Yet, Pfizer in its application stated:

1. An issued patent is valid, in the absence of any evidence to the contrary.
Patent Act, R.S.C., 1985, c. P-4, s. 45 (the "Act")

2. It is "well settled" that the presumption of validity governs the allocation of the burden of proof in a section 6 application under the PM(NOC) Regulations:
   a) the first person (in this case, Pfizer) has the burden of establishing that the second person's (in this case, Ratiopharm's) allegations of invalidity are not justified;
   b) because of the presumption of validity, the first person can meet that burden *merely by proving the existence of the patent*; and
   c) once the patent has been proved, the burden shifts to the second person to prove that the patent is invalid, on a balance of probabilities.

(A.R. Vol. 8 p. 1940)

[10] The issue of the interaction of s. 46 of the Act and the NOC Regulations has been dealt with on numerous occasions by this court (see *Pfizer Canada Inc*. v. *Apotex Inc*. (2002), 22 C.P.R. (4th) 466, 2002 FCT 1138 at para 82 and 83 per Dawson J; *Abbott Laboratories* v. *Canada (Minister of Health)* (2004), 36 C.P.R. (4th) 437 at paras 103-106 per Gibson J; aff'd (2005), 339 N.R. 277, 2005 FCA 250; *GlaxoSmithKline Inc*. v. *Genpharm Inc.* (2003), 30 C.P.R. (4th) 360, 2003 FC 1248 at para 45 per Heneghan J; *Janssen-Ortho Inc*. v. *Novopharm Ltd*. (2004), 35 C.P.R. (4th) 353, 2004 FC 1631 at paras 13-21 per Mosley J.; *Sanofi-Synthelabo Canada Inc*. v. *Apotex Inc*. (2005), 39 C.P.R. (4th) 202, 2005 FC 390 at 209 per Shore J.). All these cases stand for the proposition that the applicant must demonstrate, on a balance of probabilities, that the respondent's allegations of non-infringement or invalidity of the patent are not justified. The applicant has the overall legal burden of proof. Nevertheless, the respondent, as the entity which has made the allegations in the NOA, has the obligation to put these allegations "in play", i.e. to ensure there is sufficient evidence

of these allegations by which to present issues for examination by the court (*Eli Lilly & Co*. v. *Nu-Pharm Inc.* (1996), 69 C.P.R. (3d) 1, [1996] F.C.J. No. 904 (F.C.A.) (QL)).

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

[12] The law is quite settled on this point and the interpretation given by the Applicant, based on a single paragraph of a Federal Court of Appeal decision, taken out of context, does not convince me to accept a departure from accepted jurisprudence.

EXPERTS

[13] Each side marshalled a number of well qualified experts. Pfizer's experts included Dr. Gerald Brenner and Dr. Stephen Byrn.

[14] Dr. Brenner is a Pharmaceutical Chemist who holds a Ph.D. in organic chemistry from the University of Wisconsin. He worked at Merck for 33 years and his last position was the Senior Director of Pharmaceutical Research and Development, and the Department Head for Pharmaceutical Research. Since retirement, he has worked as a consultant.

[15] Dr. Byrn holds a Ph.D. as a Physical Chemist and has worked at Purdue University in Indiana for over 30 years. He has authored numerous textbooks and book chapters on the solid state chemistry of drugs, and published over 100 scientific papers in the area of physical chemistry.

[16] Ratiopharm's experts included Dr. Robert Miller, Dr. Eli Shefter, and Dr. Stephen Houldsworth.

[17] Dr. Miller holds a Ph.D. in Pharmaceutics from Temple University in Philadelphia. He was employed by Merck for two years and responsible for pharmaceutical product formulation. He then worked for Novopharm performing pharmaceutical product formulation, manufacturing process design, and manufacturing technical support. From 1994 to 2002, he taught at the University of British Columbia.

[18] Dr. Shefter holds a Ph.D. in Pharmaceutics and has published over 100 papers on a variety of pharmaceutical topics. He has conducted research on crystal structure and the pharmaceutical activity of dihydropyridines. He is now a self-employed consultant for pharmaceutical and biotechnology companies, an adjunct professor at the University of California, and the Chief Scientific Director for a company providing product development services.

[19] Dr. Houldsworth holds a Ph.D. in Organic Chemistry from the University of Nottingham, England and is the Operations Team Leader at Dalton Chemical Laboratories Inc. He is responsible for the day-to-day operation of the company and serves as project manager for many contracts.

[20] This case does not turn on expert evidence. On all the key points, the experts are in agreement. Their evidence only differs on what a person skilled in the art would have anticipated or considered obvious. Ultimately, these are questions for the court to decide. Therefore, although the expert evidence is useful, it is not determinative. Accordingly, I will treat the expert evidence in the same way as Justice Campbell in *A B Hassle* v. *Apotex* (2003), 27 C.P.R. (4th) 465, 2003 FCT 771:

> 16 Each of the expert witnesses to the present case has sworn that the evidence they have provided is true. On this basis, an evaluator of the evidence must start from the proposition that the witnesses are credible unless good cause is shown, and can be articulated, to the contrary (for an example of this general principle see: *Maldonado* v. *Canada (Minister of Employment and Immigration)*, [1980] 2 F.C. 302 (C.A.). That is, while they might hold differing views on a given topic, it must be assumed that they are not just saying things to bestow a benefit on the party who is relying on their evidence. In my opinion, it is unfair to the witnesses and, accordingly, to each of the parties, to make negative credibility findings in the guise of findings of weight without seeing and hearing each witness testify.
>
> 17 I have absolutely no reason to question the credibility of each of the experts in the present case.

PATENT CONSTRUCTION

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

> It is a pre-requisite to considerations of both patent validity and infringement that the language of what is claimed in the patent be properly considered. The Court can do no better than to take the same approach in an NOC proceeding, keeping in mind the restricted purpose of the proceeding. The Supreme Court has done much to codify and clarify patent claim construction in two recent cases handed down the same day: *Free World Trust* v. *Électro-Santé Inc*., [2000] 2 S.C.R. 1024 and *Whirlpool Corp*. v. *Camco Inc*., [2000] 2 S.C.R. 1067. The reasons in both were given by Mr. Justice Binnie. I take the following principles as having particular relevance to this case:
>
> 1. A patent is construed as a bargain between the inventor and the public. In consideration of disclosing the invention, the inventor is given a temporary monopoly to exploit it.
>
> 2. It is a statutory requirement that the patent contain a specification and end with a claim or claims "defining distinctly and in explicit terms the subject-matter of the invention for which an exclusive privilege or property is claimed". The specification must be sufficiently full, clear, concise and exact "as to enable any person skilled in the art or science to which it pertains, or to which it is most closely connected, to make, construct, compound or use it". (*Patent Act*, R.S.C. 1985, c. P-4, as amended, s. 27)

> 3. The patent is notionally addressed to a person skilled in the art or science of the subject-matter and is to be read as such a person would have read it when it first became public. (More will be said about this skilled reader.)
>
> 4. The claims are to be read in an informed and purposive way to permit fairness and predictability and to define the limits of the monopoly "[I]ngenuity of the patent lies not in the identification of the desired result but in teaching one particular means to achieve it. The claims cannot be stretched to allow the patentee to monopolize anything that achieves the desired result" (*Free World Trust*, paras. 31, 32).
>
> 5. The claim portion of the patent specification takes precedence over the disclosure portion in the sense that the disclosure is read to understand what was meant by a word in the claims "but not to enlarge or contract the scope of the claim as written and thus understood" (*Whirlpool*, para. 52).
>
> 6. It is only such novel features that the inventor claims to be essential that constitute the "pith and marrow" of the claim. "The key to purposive construction is therefore the identification by the Court with the assistance of the skilled reader, of the particular words or phrases in the claims that describe what the inventor considered to be the "essential" elements of his invention" (*Whirlpool*, para. 45).
>
> 7. Some elements of the claimed invention are essential and others are not, based either on common knowledge when the patent was published or according to the intent of the inventor, expressed or inferred from the claims. This lies at the heart of Biovail's position that Novopharm's allegation that it will not infringe the '320 patent is not justified. Put another way, was it obvious at the time the patent was published that the substitution of a variant would make a difference?
>
> 8. To overclaim is to lose everything. If the inventor underclaims, the court will not broaden the monopoly in the interests of the "spirit" thereof. This often, as in this case, results in layers of claims, each limitation serving as a potential safety net so that if the broadest claims fall, the monopoly may be saved in part by the more modest claims.
>
> 9. Yet a patent is not an ordinary writing. It meets the definition of a "regulation" in the Interpretation Act, and must be read to assure the attainment of its objects. "Claims construction is a matter of law for the judge, and he was quite entitled to adopt a construction of the claims that differed from that put forward by the parties." (*Whirlpool*, para. 61.)

[22] The only claim in issue is claim 11 of the 393 Patent which reads as follows:

> “The besylate salt of amlodipine”

Thus, the only thing that is claimed is the besylate salt of amlodipine. No claim is made regarding the selection that led to the besylate salt of amlodipine, its properties, its use, or its state.

[23] The disclosure of the 393 Patent points out that besylate was selected because of its unusual combination of desirable properties when preparing pharmaceutical formulations in terms of solubility, stability, non-hygroscopicity and processability (stickiness). The examples then teach two

methods on how to prepare a besylate salt of amlodipine, and how to formulate tablets, capsules and sterile aqueous solutions.

[24] The disclosure further reveals that besylate was tested against eight other pharmaceutically acceptable salts of amlodipine in respect of solubility, stability, non-hygroscopicity and processability (stickiness) and then ranked them as follows:

Solubility and pH (combined)
1. acetate
2. besylate
3. salicylate

Stability
1. besylate
2. mesylate
3. tosylate

Non-hygroscopicity
1. maleate (tied)
1. besylate (tied)
3. tosylate

Processability
1. mesylate
2. besylate
3. tosylate

On the basis of these tests, the disclosure teaches that the besylate is an outstandingly suitable candidate for the pharmaceutical preparations of amlodipine given its overall ranking in all four categories.

SUFFICIENCY OF NOA

[25] Pfizer alleged in the oral argument before me that the NOA is insufficient as it:

1. Makes no reference to the testing regarding stability that Ratiopharm commissioned from Dalton Chemical Laboratories Inc. regarding the stability of maleates (the "Dalton Testing");

2. It fails to make reference to s. 34(1) of the Act, yet Rationpharm's pleadings point to the failure to comply with s. 34(1); and

3. It does not contain the allegation to support paragraph 95 of Ratiopharm's pleadings that "the limited number of salts tested in the 393 patent were purely selected to make besylate appear advantageous".

[26] The Dalton Testing was conducted on Ratiopharm's behalf in December 2003 to test the stability of the besylate and maleate salts of amlodipine. It involved the following:

> In December 2003 Dalton Chemical was retained by ratiopharm Limited of Mississauga, Ontario ("ratiopharm") to conduct thermal stability studies on the raw active pharmaceutical ingredient ("API") amlodipine besylate and amlodipine maleate and 10 mg tablet formulations of that API (the "ratiopharm Retainer"). Specifically, Dalton Chemical was contracted to conduct degradation tests (the "Degradation Tests") on the API and tablet formulations at two temperatures (50°C and 75°C) at ambient humidity. The API and the tablets were to be analyzed using high performance liquid chromatography ("HPLC") at time zero and after one week's, two weeks' and three weeks' storage under the two temperature conditions. The purpose of the Degradation Tests of the API was to measure the number and amount (percentage of the active ingredient) of breakdown products at specified time points. The purpose of the Degradation Tests of the tablet formulations was to measure the number and amount (percentage of the claim on the label of the active ingredient) of breakdown products.
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> (Dr. Houldsworth's affidavit A.R. Vol. 6 tab 12 p. 1557)

[27] It is well established that the NOA and the detailed statement of legal and factual basis for the allegation must provide all the facts the generic producer intends to rely upon in subsequent prohibition proceedings. The maker of the NOA cannot rely on facts that exceed those laid out in its detailed statement (see *Procter & Gamble Pharmaceuticals Canada, Inc.* v. *Canada (Minister of Health)*, [2003] 1 F.C. 402, 2002 FCA 290 at para 21 to 26).

[28] In its NOA, Ratiopharm contended that besylate offers no advantage over maleate in terms of stability over the follow terms:

> With respect to stability, there is no disclosure of the number and amount of each impurity and no disclosure of the degree of difference in stability between the salts tested from which it could be concluded that a substantial advantage is secured by the besylate salt. As at the date of the '393 Patent., the standard test for impurity quantification employed by high performance liquid chromatography (HPLC). No HPLC test results are reported in the '393 Patent. The thin layer chromatography (TLC) test results reported in the '393 Patent results are qualitative in nature. In fact, the besylate salt offers no substantial or practically significant improvement in stability over any of the other salts tested, and in particular, offers no substantial or practically significant improvement in stability over the maleate salt of amlodipine identified in the prior art as being particularly preferred.
>
> (A.R Vol. 1 p. 29)

[29] There is no reference to the Dalton Testing or its result in the NOA. Yet, the Dalton Testing was done in December 2003 and the NOA is dated May 2004. The Dalton Testing results represent new facts that should have been alleged in the NOA so that Pfizer could have produced its own countertest should it have so chosen. Not having been apprised of the Dalton Testing in the NOA (except by the oblique indirect reference above cited), Ratiopharm cannot now rely on such tests to impugn the findings of stability of besylate. Applying and following *Mayne Pharma (Canada) Inc* v. *Aventis Pharma Inc.* (2005), 38 C.P.R. (4th) 1, 2005 FCA 50 at para 21 and *Aventis Pharma Inc.* v. *Apotex Inc*. (2005), 43 C.P.R. (4th) 161, 2005 FC 1283 para 305, I shall disregard the Dalton Testing evidence.

[30] Peripherally, I might add that the Dalton Testing results would not have greatly advanced Ratiopharm's case as by the admission of its own witnesses:

a) the results at 50 degree are anomalous and cannot be scientifically explained;
(Dr. Miller affidavit A.R. Vol. 6 Tab 10 p. 1500)

b) the tester used the wrong version of the protocol and no explanation for this is provided; and
(Dr. Houldsworth's cross-examination A.R. Vol. 7 Tab 18 p.1907)
(Dr. Shefter's cross examination A.R. Vol. 7 Tab 17 p. 1860)

c) the test results from only one machine are reported, yet two machines were used. No evidence is provided as to the results from the second machine or why they have not been furnished.
(Dr. Houldsworth's cross examination A.R. Vol. 7 Tab 18 p. 1907)

[31] With respect to s. 34(1) of the *Patent Act*, R.S.C. 1985, c. P-4, which is also known as the pre-1989 Patent Act (the "Old Act"), I fail to see the merit of Pfizer's allegation. Section 34(1) provides

> 34(1) An applicant shall in the specification of his invention
> (a) correctly and fully describe the invention and its operation or use as contemplated by the inventor.

[32] Section 34 requires that the specification disclose the invention. Whether a specification adequately discloses the invention is to be considered from the perspective of a workman of ordinary skill in the art. Two things must be described in the disclosure of a specification: 1) the invention and 2) the operation or use of the invention. For a selection patent, it is necessary to disclose in the specification the special advantages that the special members of the class possess (see *Sanofi-Synthelabo, supra* at para 56).

[33] Ratiopharm alleges that the disclosure in the 393 Patent fails to show whether the besylate salt has any special stability property of any material significance over the other acid addition salts tested. It does not identify any special property that is surprising or unexpected over the other acid addition salts that would support the conclusion in the 393 Patent that it is any more "outstandingly suitable for the preparation of formulations of amlodipine" than any other of the salts evaluated. The fact that it did not cite s. 34(1) is of no import. The NOA makes it clear that Ratiopharm challenges the 393 Patent on the basis, *inter alia*, of not being a valid selection patent, which is an indirect way of saying that it does not comply with s. 34(1).

[34] As to the third point in paragraph 25, this is implicit in a challenge that the 393 Patent is an improper selection patent. Thus, there is no need to set this out specifically in the NOA. Either it is a valid selection patent or not; the motives for the selection are not at issue.

ANTICIPATION

[35] Pfizer alleges that the 393 Patent was anticipated by the European counterpart of the 865 Patent which is the European Patent Application 0089167 (the "EPA"). It is not disputed that the EPA predates the 393 Patent by more than two years. Subsection 27(1) of the Old Act reads:

> 27 (1) Subject to this section, any inventor or legal representative of an inventor of an invention that was
>
> (a) not known or used by any other person before he invented it,
>
> (b) not described in any patent or in any publication printed in Canada or in any other country more than two years before presentation of the petition hereunder mentioned, and
>
> (c) not in public use or on sale in Canada more than two years prior to his application in Canada, may, on presentation to the Commissioner of a petition setting out the facts, in this Act termed the filing of the application, and on compliance with all other requirements of this Act, obtain a patent granting to him an exclusive property in the invention.

[36] The law in respect of anticipation and selection patents was recently summarized by my colleague Justice Shore in *Sanofi-Synthelabo, supra* where he stated in paragraph 55 and 56:

> 55 Anticipation means that the exact invention had already been made and publicly disclosed. The test for anticipation was described in *Beloit,* [1986] F.C.J. No. 87, and adopted by the Supreme Court of Canada in *Free World* [at para 26]:
>
> > One must, in effect, be able to look at a prior, single publication and find in it all the information which, for practical purposes, is needed to produce the claimed invention without the exercise of any inventive skill. The prior publication must contain so clear a direction that a skilled person reading and following it would in every case and without possibility of error be led to the claimed invention. (Emphasis added.)
>
> The choice of the phrase "in every case and without possibility of error" is an important choice of words. The mere possibility that one could be within the claim is not, in and of itself, sufficient for anticipation.

...

As was decided by this Court in *Pfizer Canada Inc*. v. *Apotex Inc.* [See Note 27 below], a claim to a specific chemical compound cannot be anticipated by a prior art reference which only teaches a broad class or genus of compounds into which the compound falls because the prior art reference does not give directions which inevitably result in the specific compound.

56 With respect to the identification of specific beneficial properties in a particular compound selected from a more general class of compounds, Fox in Canadian Law and Practice (4th edition) at pages 89-90 states the following:

> Invention may be exercised by selecting one out of a number of substances for a particular purpose even though others of that class have been used before for the same purpose, provided there is a special advantage to be derived from the use of the selected substance and its selection constitutes a definite advance upon existing knowledge. While one who merely picks out a number of items from an already disclosed group or series has not invented anything, yet it may be otherwise if his researches have led him to the discovery that certain items in the group or series possess qualities or characteristics peculiar to themselves and hitherto unknown. (Citations omitted and emphasis added.)

In Re E.I. Du Pont Nemours & Co. Application [See Note 28 below], the House of Lords, in regard to newly identified beneficial properties, held:

> The law regarding selection patents has been developed to deal with this problem... The present position was compendiously stated by Lord Diplock:
>
> > ... The inventive step in a selection patent lies in the discovery that one or more members of a previously known class of products possess some special advantage for a particular purpose, which could not be predicted before the discovery was made... The quid pro quo for the monopoly granted to the inventor is the public disclosure by him in his specification of the special advantages that the selected members of the class possess. (*Beecham Group* v. *Bristol Laboratories International S.A.* [1978] R.P.C. 521 at 579). (Emphasis added.)

[37] Thus, the question becomes was a person skilled in the arts given such a clear direction by the EPA that in every case, and without possibility of error, he would make the salt claimed in the 393 Patent, *i.e*. the besylate salt of amlodipine?

[38] Before applying these principles to the 393 Patent, the court notes that there is no dispute as to the following facts:

a) the EPA and the 865 Patent claim the discovery of certain 1,4 dyhydropyridines (which include amlodipine) and their pharmaceutically acceptable salts;

b) the EPA and the 865 patent disclose the use of said 1,4 dyhydropyridines (which include amlodipine) and their pharmaceutically acceptable salts as an anti-ischaemic or anti-hypertensive agent together with a pharmaceutically acceptable carrier;

c) pharmaceutically acceptable salts (given that amlodipine is a base) refers to the 80 anions identified in the seminal article of Stephen Berge of January 1977 ("Berge") in the Journal of Pharmaceutical Sciences entitled "Pharmaceutical Salts" which lists approximately 80 salts including besylate.

[39] Salt selection is a difficult and time consuming process. Dr. Brenner describes it as follows:

> Many drugs are pharmaceutically active in their un-ionized (free) form; they do not need to form salts in order to exhibit their desired physiological effects. However, salt forms can change the properties of the parent molecule, including physical and chemical properties that can have a positive influence in the development of a commercial dosage form. For free acids or bases that do not have optimal properties for formulation, salt selection can be used to change or improve them. Many different properties of a drug can be altered or optimized by the salt selection process.
>
> •••
>
> Some drugs in their free acid or base forms will exist at room temperature as oils (for example, once of the salts in example 18 of the European Application) or as solids with low melting points. Oils are not easy to purify and are not easy to work with. Other drugs in their free forms will exist at room temperature as "amorphous" solids. These are easier to handle than oils, but they are not easy to purify. Purification— *e.g.*, by crystallization – is important in pharmaceutical development for at least a couple of reasons: the drug is freed from potentially toxic impurities; and for drugs that are less than optimally stable, the purer the drug typically the more stable it tends to be.
>
> Many salts exist as crystalline solids at room temperature. For pharmaceuticals, this is the optimal form not only because crystals are easier to handle than oils, but also because crystallization is the major purification process applied to drugs.
>
> The higher melting point of many salts is also desirable in commercial pharmaceutical formulation. In the tablet-making process, for example, a drug is subjected to pressures that are high enough to generate heat and cause melting. The higher the melting point of the drug, the more robust it will be for tablet manufacturing purposes. I note from the disclosure of the European Application that the free base of amlodipine would not be acceptable for preparing a tablet formulation because the melting point is too low (79-80°C). One would want to select an amlodipine salt with a higher melting point. Based on the discloser of the '393 Patent, amlodipine besylate would be an example of such a salt. The disclosure indicates that the besylate salt has a melting point of 201°C.
>
> As my examples illustrate, salt selection is a very important part of the pharmaceutical development process because it offers the opportunity to tailor the properties of the drug to a particular purpose.

> For the commercial formulation of tablets, for example, salt selection can be used to optimize the combination of properties important to this process, including stability, non-hygroscopicity, solubility, melting point, handling and others.
>
> Despite the importance of salt selection, there has never been a way to determine how a given acid will behave in combination with a given molecule, what properties any resulting salt will have, or which particular salt of a drug will be the best for a given purpose. The characteristics of salts are unpredictable and have always been so. Salt selection has thus been described – accurately in my opinion – as 'a difficult empirical task": see the well known review article entitled "Pharmaceutical Slats" by S.M. Berge *et al.* in *J. Pharm. Sci*. (1977), 66:1-19, ...

(Dr. Brenner's affidavit A.R. Vol. 4 Tab 4 p 1063)

This evidence was not challenged on cross examination.

[40] Similarly, while there are 80 pharmaceutically acceptable salts on the Berge table, this does not simply mean 80 tests; rather, it means millions of tests. As Dr. Byrn noted in his affidavit, which also was not challenged:

> The skilled person would have no indication from the existence of besylate salts of other compounds about the prospects of amlodipine besylate having a desirable combination of properties for pharmaceutical formulation.
>
> The proposition, if indeed this is Ratiopharm's proposition, that it is obvious to make every possible pharmaceutically acceptable salt of a given compound and test them all to find out which is the best one, is in my opinion unreasonable. In addition to the numerous syntheses of the salts themselves and the extensive testing for physicochemical properties, once has to deal with the crystal properties of the salts. To do this, once would need to perform extensive crystallization experiments under varying conditions – that is, with different solvents, at different temperatures, with different concentrations and at different evaporation rates – to identify a stable, crystalline form. Millions of experiments would be required. As a practical matter, this number of experiments would not be done, not least because the huge amount of raw material that would be needed.

(Dr. Bryn's affidavit A.R. Vol. 4 Tab 5 p. 1100)

[41] The EPA teaches that 1,4 dyhydropyridines (which includes amlodipine) and their pharmaceutically acceptable salts can be made, and uses the example of maleate to show how they are made. It also teaches that this process can be replicated with any of the 80 pharmaceutically acceptable salts referred to in Berge. However, it does not teach a skilled person:

i) why to select benzene sulphonic acid (besylate) as one of the initial choices to form an acid-addition salt for amlodipine;

ii) whether benzene sulphonic acid would form a salt of amlodipine in the solid state; or

iii) the particular properties of amlodipine besylate or their advantage for pharmaceutical formulations.

[42] In light of the foregoing, it seems apparent that a person skilled in the arts would not in every case, and without possibility of error, on the basis of the EPA make the besylate salt. Accordingly, I do not find that the EPA anticipated the 393 Patent.

VALIDITY OF SELECTION PATENT

[43] Ratiopharm contends that the 393 Patent is invalid for obviousness double patenting and is an improper selection patent. It contends that:

(a) the selection of amlodipine besylate over the prior disclosed class of pharmaceutically acceptable acid addition salts of amlodipine does not meet the criteria of a valid selection patent; and

(b) that the disclosure of the 393 Patent is insufficient to support the selection of amlodipine besylate over the other acid addition salts based on a combination of solubility, hygroscopicity, processability and stability characteristics.

[44] In *Whirlpool Corp*. v. *Camco Inc*., [2000] 2 S.C.R. 1067, 2000 SCC 67, Justice Binnie stated at para 66 and 67:

> There is, however, a second branch of the prohibition which is sometimes called "obviousness" double patenting. This is a more flexible and less literal test that prohibits the issuance of a second patent with claims that are not "patentably distinct" from those of the earlier patent....
>
> In Consolboard, supra, Dickson J. referred to Farbwerke Hoechst as "the main authority on double patenting" (p. 536) which stood for the proposition that a second patent could not be justified unless the claims exhibited "novelty or ingenuity" over the first patent …

[45] The experts for both parties agree that the 865 Patent is a genus patent that includes amlodipine bysylate. Amlodipine is expressed in claim 12 of the 865 Patent in organic chemistry nomenclature (see Dr. Shefter's affidavit A.R. Vol. 6, Tab 11, p. 1519 at para 12; Dr. Byrn cross-Examination A.R. Vol. 5, Tab 9, p. 1421, q. 130 to 132).

[46] Unless the patent can be characterized as a selection patent, the concept of obviousness double patenting as enunciated by Justice Binnie in *Whirlpool, supra* prohibits the issuance of a second patent with claims that are not patentably distinct from a prior patent.

[47] Selection patents have their origin in *I.G Farbenindustrie A.G.'s Patents* (1930), 47 R.P.C. 289 at p. 322 where Maughan observed:

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

[48] The rationale for such policy can be found in Lord Glaisdale's observation in E.I. Du Pont de Nemours & Co. (Witsiepse's) Application, [1982] FSR 303 (H.L.) at p. 313:

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

[49] An excellent summary of the state of the law is found in the British text by T.A. Blanco White, *Patents for Inventors and the Protection of Industrial Designs*, 5th ed. (London: Stevens & Sons, 1983) at p 62, para 14-110 where it states:

> The current view is, that disclosure of a class, even a very small class, whether the disclosure is in general terms or by enumeration of the members, is not disclosure of the individual members so as to make them no longer new. In particular, mere recital of the systematic name of a chemical compound is not a publication of it: a compound is not an old compound until it has actually been made. Furthermore, an invention involving knowledge of the properties of a compound has not been made, and so cannot be published, until the compound has been not only made but tested for the properties concerned. It follows from this approach that in any ordinary selection case the question is not one of novelty but one of obviousness, utility and sufficiency of description, these in the ordinary way.

[50] A careful examination of the 393 Patent reveals that no rationale is given why the nine salts are only tested for solubility, stability, non-hygroscopicity and processability. This is astonishing given that Pfizer's own memorandum states at paragraph 24:

> One problem with amlodipine maleate was its tendency to degrade. The structure of the maleate part of amlodipine maleate allowed it to participate in a chemical process known as a Michael addition reaction (MAR). The MAR converted amlodipine maleate into a different molecule (MAR Product). The MAR Product was biologically active and, in uncontrolled concentrations, could have posed a risk to patient safety. As a result, Pfizer took the unusual step of abandoning amlodipine maleate in mid-clinical testing, and undertook research to discover an alternative and more advantageous salt.
>
> [A.R. Vol.8 para 24]

[51] No rationale is given for the selection of the threshold factors. If we look at the thresholds for each characteristic we see the following:

a) the threshold for solubility is at greater than 1 mg ml^{-1} at pH 1-7.5 (close to that of the pH of blood at 7.5). Why 1 mg ml^{-1} is not explained. Yet table 1 on page 3 of the 393 Patent shows besylate with a solubility of 4.6 while mesylate is at 25, and acetate and hydrochloride are both at 50. The pH at saturation of acetate and besylate is the same. In addition, the expert evidence makes it quite clear that the pH factor could easily be adjusted by addition of pH. Dr. Miller stated in his affidavit:

> "The Ordinary Formulator could have adjusted the pH of each of the salts by the selection of an appropriate alkaline or acidic excipient in the solid state to improve dissolution.
>
> (Dr. Miller's affidavit A.R. Vol. 6, Tab 10, p. 1499, para 47)

The threshold for solubility is thus totally unexplained.

b) the threshold for stability is not stated. To test for stability, each salt was blended in a powder vehicle (in the case of tablets, the vehicle was comprised of microcrystalline cellulose in 50:50 combination with anhydrous dibasic calcium phosphate), sealed in vials, and stored at 50° C and 75° C for up to three weeks. The salt, and any breakdown products, were then compared and ranked according to the number and amount of breakdown products that were produced. Besylate turned out to be the most stable. However, neither the magnitude of the number and quantity of the breakdown products, nor the magnitude of the difference between one salt and another was disclosed. Thus, it is impossible to tell the degree to which besylate was more stable than mesylate for instance, and whether this difference was significant. As D.r Shefter stated:

> All that can be gleaned from the disclosure in the '393 Patent with respect to stability is that the sulfonate salts (besylate, mesylate and tosylate) are more stable than the other salts evaluated (which are not sulfonate salts), and that the besylate salt is the most stable of the sulfonate salts. As a result, the disclosure fails to show whether the besylate salt has any special stability property of any material significance over the other salts evaluated. The '393 Patent identified that amlodipine maleate, the preferred salt form of amlodipine disclosed in the European Application raised concerns with respect to stability as it tended to break down in solution after a few weeks. If the stability of the pharmaceutically acceptable acid addition salts of amlodipine would therefore have been of concern to the inventors named in the '393 Patent, I would have expected the inventors to quantify the stability properties of the salts evaluated in the '393 Patent and for the '393 Patent to specify the degree to which the besylate salts possessed the most stable properties of the salts evaluated.
>
> (Dr. Shefter affidavit, A.R. Vol. 6, Tab 11, p. 1535, para 41)

c) the threshold for non-hygroscopicity was that the salt had to remain unanhydrous when exposed to 75% relative humidity at 37° C for 24 hours and when exposed to 95% relative humidity at 30° C for three days. No rationale is provided why these parameters were chosen, or why all three parameters were changed for the second experiment. Furthermore, as Dr. Miller states in his affidavit:

> In my opinion the test at 95% humidity is an extreme test because it is exposing the salt to essentially a wet condition. A standard test for hygroscopicity would be to expose the salt to 75% humidity. In my opinion, the results of the test at 95% relative humidity cannot be used to predict that the tosylate salt would not be anhydrous in tablet form. In my opinion, there is no practical pharmaceutical difference to the hygroscopicity among the maleate, tosylate and besyalte salts of amlodipine. Furthermore, the patent does not disclose the degree to which the other salts of amlodipine picked up water in the test at 75% relative humidity. It is possible that the other salts only picked up a very small quantity of water in which case there would be no practical pharmaceutical difference between those other salts and the maleate, tosylate and besylate salts.
>
> (Dr. Miller affidavit A.R. Vol. 6 Tab 10, p. 1501, para 57)

d) the threshold for processability is set out as meeting the degree of stickiness to a tablet punch that maleate exhibits. No rationale is provided why the maleate was considered to represent the ideal degree on non-stickiness, nor why the relative minute difference are so significant, nor why they could not be fixed by addition of a lubricant. As Dr. Shefter observed:

> The test for stickiness disclosed in the '393 Patent has little meaning for a number of reasons. First, the amount of amlodipine in the tablet material that stuck to the tablet punch is very small for each of the salts evaluated. In my opinion, the differences between these amounts would be insignificant from a practical perspective. As of the publication of the European Application in 1983, the Skilled Formulator would have recognized the need to include a lubricant such as magnesium stearate in a commercial tablet formulation and would have adjusted the tablet formulation to achieve good compressability and lubricity and thereby eliminate virtually all stickiness.
>
> In fact, the '393 Patent acknowledges that good compressability of a tablet can be achieved using suitable diluting excipients ('393 Patent, p. 5). Furthermore, the 5 mg and 10 mg formulations of amlodipine besylate that Pfizer makes available include the excipient magnesium stearate (Lombardi Affidavit, Exhibit B-49). If the superiority of the processablity properties of the amlodipine besylate was surprising and significant, Pfizer would not have had to include a lubricant such as magnesium stearate in its commercial formulation of amlodipine besylate.

(Dr. Shefter affidavit A.R. Vol. 6, Tab 11, pp. 1539-1540, paras 52-53)

[52] As can be seen from the forgoing analysis, all four factors had a totally unexplained minimum threshold. No evidence was presented to show that any of the four characteristics were not known beforehand. Similarly, no evidence was provided to justify the minimum threshold in terms of regulatory requirements, industry standards, ease of production, or minimization of costs. The 393 Patent only verified the extent of the characteristic and compared it to nine other salts. Meeting or surpassing these minimum thresholds (which Ratiopharm claims were arbitrarily set) is described in the 393 Patent in the following manner:

> It has now unexpectedly found that the benzene suphonate salt (hereinafter referred to as the besylate salt) has a number of advantages over the known salts of amolodipine and, additionally has unexpectedly been found to have a unique combination of good formulation properties which make it particularly suitable for the preparations of pharmaceutical formulations of amlodipine

[53] However, in my view it is nothing of the sort. Any combination of the four characteristics in the nine salts can qualify as unique, and as being particularly suitable for pharmaceutical preparations of amlodipine, so long as no rationale is given for choosing the minimum threshold. Any alteration of these thresholds could result in another salt having "a unique combination of good

formulation properties which make it particularly suitable for the preparations of pharmaceutical formulations of amlodipine". In effect, these thresholds can be manipulated to get the outcome one desires.

[54] The purpose of selection patents is to reward the inventor for discovering hitherto unknown characteristics peculiar to the members of the selection. The purpose is not to permit the creation of valid selection patents simply by allowing an 'inventor' to test the degree of known characteristics, setting unexplained minimum thresholds without any justification, and then claiming any product that meets the combination of these characteristics is unique.

[55] What Pfizer did in this case, in essence, amounts to no more than verifying that besylate has the following degree of:

a) solubility: 4.6 mg ml^{-1}, pH 6.6;

b) stability: it is most stable amongst Hydrochloride, Acetate, Maleate, Salicylate, Succinate, Tosylate, Mesylate and Besylate;

c) Non-hygroscopicity: it remains non-hygroscopic when exposed to 90° C for three days; and

d) Processability: 1.17 μg Amlodipine cm -2, i.e. 58% relative to maleate.

It is trite law that verifying existing properties or their degree is not inventing (see H.G. Fox, *The Canadian law and Practice Relating to Letters Patent for Inventions* (4th ed) (Toronto: The Carswell Company Limited, 1969), p. 90). In this case, there is no "substantial advantage to be secured by the use of the selected members" nor is there a "quality of a special character which can fairly be said to be peculiar to the selected group" as required by the threefold test of *I G Farbenindustrie, supra.*

[56] As far as the 'unique combination' of these characteristics is concerned, in a case such as the present one where there is no rationale for either the selection of the characteristics or the thresholds chosen, I have to agree with the logic of Ratiopharm's submission which states:

> Pfizer contends that the unique combination of the formulation properties of amlodipine besylate cannot be predicted and therefore possess an unexpected advantage. If this contention is correct it would lead to the absurd result that the selection of any [salt] of an AI and the verification of its properties could be patentable. Any selected salt could be tested for any of a number of properties which could conceivably support a claim to "unique properties" that could not be predicted. Pfizer's contention must therefore be rejected.
>
> (R.R. amended factum para 87)

[57] Accordingly, the 393 Patent is not a valid selection patent, and Pfizer has failed to disprove Ratiopharm's allegation that the 393 Patent is invalid for obviousness double patenting.

[58] In light of the foregoing finding, there is no need to address Ratiopharm's allegation of obviousness.

ORDER

THIS COURT ORDERS that that this application be dismissed with costs to the Respondents.

Judge

FEDERAL COURT

NAMES OF COUNSEL AND SOLICITORS OF RECORD

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