Federal Court  Cour fédérale

Date: 20111206

Dockets: T-644-09
T-933-09

Citation: 2011 FC 1486

Ottawa, Ontario, December 6, 2011

PRESENT: The Honourable Mr. Justice Boivin

Docket: T-644-09

BETWEEN:

APOTEX INC.

Plaintiff

and

SANOFI-AVENTIS

Defendant

Docket: T-933-09

BETWEEN:

SANOFI-AVENTIS AND
BRISTOL-MYERS SQUIBB SANOFI
PHARMACEUTICALS HOLDINGS
PARTNERSHIP

Plaintiffs

and

APOTEX INC.
APOTEX PHARMACHEM INC.
AND SIGNA SA de CV

Defendants

PUBLIC REASONS FOR JUDGMENT

Heard: April 18, 19, 20, 21, 26, 27, 28, 29,
May 3, 4, 5, 9, 10, 11,
May 16, 17, 18, 19, 24, 25, 30, 31,
June 1, 13, 14, 15, 2011

I Introduction

A. *Preliminary Observations*

[1] This case concerns the drug clopidogrel bisulfate, sold in Canada under the brand name Plavix and commercialized as an anticoagulant that inhibits platelet aggregation activity in the blood. Plavix is the subject of Canadian Patent No. 1,336,777 (the '777 Patent) issued on August 22, 1995.

[2] The '777 Patent is a selection patent held by Sanofi-Aventis.[1] At the heart of this case lies the issue of the validity of the '777 Patent. Sanofi submits that the '777 Patent is valid and that it has been infringed by Apotex[2] who manufactures and sells generic clopidogrel. Apotex, on the other hand, submits that the '777 Patent is invalid and that there has accordingly been no infringement.

[3] The application leading to the '777 Patent was filed in Canada on February 2, 1988. The Court observes at the outset that pursuant to s 78.1-78.2 of the current *Patent Act*, RSC 1985, c P-4, as amended, patent applications, such as the one at issue, filed before October 1, 1989 are to be dealt with under the provisions of the *Patent Act* as they read immediately before that date.

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[1] In these reasons, the Court will refer to Sanofi-Aventis and Bristol-Myers Squibb Sanofi Pharmaceuticals Holdings Partnership collectively, as "Sanofi".

[2] In these reasons, the Court will refer to Apotex Inc. and Apotex Pharmachem Inc. collectively, as "Apotex".

Thus, references in these Reasons to the *Patent Act* (referred to as the *Patent Act* or the Act), unless specifically noted otherwise, will be to the Act as it stood immediately prior to October 1, 1989.

[4] The Court further notes that this proceeding in fact consists of a consolidation of two actions. First, there is the impeachment action undertaken by Apotex (T-644-09) and, second, there is the infringement action undertaken by Sanofi (T-933-09). The procedural background in which each of these actions was initiated is summarized next.

B. *Procedural Background*

[5] On March 10, 2003, Apotex served upon Sanofi a Notice of Allegation (NOA) under the *Patented Medicines (Notice of Compliance) Regulations*, SOR/93-133 (PMNOC Regulations) for the purpose of obtaining a Notice of Compliance (NOC) from the Minister of Health, pursuant to section C.08.004 of the *Food and Drug Regulations*, CRC 1978, c 870. As part of its NOA, Apotex alleged that its manufacture and sale of generic clopidogrel bisulfate tablets would not infringe any valid claim in the ‘777 Patent.

[6] In response, Sanofi sought an order prohibiting the Minister of Health from issuing a NOC to Apotex in respect of generic clopidogrel bisulfate tablets until the expiry of the ‘777 Patent.

[7] By Order dated March 21, 2005, Justice Shore of the Federal Court granted Sanofi’s application. As a result of this Order, the ‘777 Patent prevented Apotex from coming to market with its generic clopidogrel bisulfate tablets in Canada. The Federal Court of Appeal and the Supreme

Court of Canada upheld this Order. Apotex accordingly did not obtain a NOC from the Minister of Health.

[8] Following the Order dated March 21, 2005, and related court challenges, the two present actions, now consolidated, were commenced as follows: Apotex' impeachment action dated April 22, 2009 (T-644-09); and Sanofi's infringement action dated June 8, 2009 (T-933-09).

[9] In summary, Apotex' impeachment action seeks a declaration that the claims of the '777 Patent are invalid, void and of no force and effect. Apotex alleges the following grounds of invalidity:

- inutility;
- lack of demonstrated utility/lack of sound prediction;
- obviousness;
- lack of novelty/anticipation;
- double patenting.

Apotex further seeks a declaration of non-infringement with respect to its generic clopidogrel products.

[10] Conversely, Sanofi's infringement action seeks a declaration that Apotex has infringed the '777 Patent by manufacturing clopidogrel – containing products in Canada for export to other countries, including the United States and that, as a result, Sanofi is entitled to injunctive relief and an accounting of profits or damages.[3]

[3] The Court notes that, initially, the infringement action was also brought against Signa but was discontinued against Signa on September 14, 2009.

[11] Apotex' impeachment action and Sanofi's infringement action were briefed as follows:

Impeachment Action

1. Apotex Statement of Claim dated April 22, 2009;
2. Apotex Amended Statement of Claim dated May 27, 2009;
3. Sanofi Statement of Defence dated June 8, 2009; and
4. Apotex Reply dated June 18, 2009.

Infringement Action

1. Sanofi Statement of Claim dated June 8, 2009;
2. Apotex Second Amended Statement of Defence and Counterclaim dated December 14, 2010;
3. Statement of Particulars dated December 2, 2010 to the Amended Statement of Defence and Counterclaim of Apotex;
4. Statement of Particulars dated December 16, 2010 bis;
5. Sanofi Reply and Defence to Counterclaim dated January 31, 2010;
6. Statement of Particulars dated April 8, 2010 in Reply to Defence to Counterclaim of Sanofi; and
7. Apotex Amended Reply to Defence to Counterclaim dated April 15, 2011.

[12] On or about July 15, 2009, Sanofi filed a motion to consolidate the impeachment and infringement actions in order for them to be heard together. Apotex indicated its opposition to consolidation in its Statement of Defence and Counterclaim and stated that the infringement action should be stayed. By Order dated November 2, 2009, Prothonotary Tabib, acting as the Case Management Judge, ordered consolidation. She further ordered bifurcation of the damages issues.

[13] Both actions were accordingly heard together in a trial that commenced on April 18, 2011. During the twenty-six (26)-day trial, a total of twenty-three (23) experts and fact witnesses appeared before the Court. A brief overview of the experts and fact witnesses' testimony is included in Appendix A.

[14] The key questions to be addressed in this proceeding are as follows:

A) Does Sanofi have standing to bring its infringement action?
B) Has Apotex infringed the '777 Patent?
C) Is the '777 Patent valid?

[15] As explained in these Reasons, the Court has concluded that:

A) Sanofi has standing to bring its infringement action;
B) The '777 Patent was infringed by Apotex; and
C) The '777 Patent is invalid.

[16] As a result, Apotex' impeachment action is allowed and Sanofi's infringement action is dismissed.

II Table of Contents

[17] To assist the reader, the Court has compiled a Table of Contents for these Reasons with page numbers for each heading.

Table of Contents **Paragraph**

III NOC Proceedings

[18] As noted earlier, the parties' dispute regarding the '777 Patent was the subject of a NOC proceeding. Given the circumstances, the Court considers it apposite to provide a brief overview of these NOC proceedings.

[19] Essentially, NOC proceedings consist of a summary procedure for assessing the validity of a Canadian patent. Such proceedings are initiated by way of application to the Federal Court of Canada (*Sanofi-Synthelabo Canada Inc. v Apotex Inc.*, 2005 FC 390, 39 CPR (4th) 202). In particular, there is no *viva voce* testimony from witnesses, and the evidence is accordingly limited to a documentary record. Significantly, the PMNOC Regulations do not allow any determinative findings on the validity of the patent *per se*; the only conclusion to be drawn in the context of NOC proceedings is whether the allegations of patent invalidity are "justified" or "not justified".

[20] Furthermore, the PMNOC Regulations do not displace the right of a patent holder to bring an action for infringement, an interested person to challenge the validity of a patent in an action for impeachment (*Pharmacia Inc. v Canada (Minister of National Health & Welfare)* (1994), [1995] 1 FC 588, 58 CPR (3d) 209 (FCA) at 217; *Bristol-Myers Squibb Co. v Canada (Attorney General)*, 2005 SCC 26, 39 CPR (4th) 449 at paras 11-12).

[21] As part of the NOC proceedings initiated by Apotex, it was alleged by Apotex that a NOC should be issued because generic clopidogrel bisulfate did not infringe the '777 Patent. In particular, Apotex maintained that the '777 Patent was invalid on grounds of obviousness, anticipation and double patenting.

[22] As noted earlier, Apotex was not successful in obtaining a NOC. Justice Shore, the Applications Judge, rejected all three (3) of Apotex' allegations of invalidity on the basis that these allegations were not justified.

[23] Apotex appealed the decision of Justice Shore and, on December 22, 2006, the Federal Court of Appeal upheld this decision and accordingly dismissed Apotex' appeal (*Sanofi-Synthelabo Canada Inc. v Apotex Inc.*, 2006 FCA 421, 59 CPR (4th) 46).

[24] Justice Noël, writing for a unanimous Federal Court of Appeal, concluded that Apotex had not shown, on a balance of probabilities, that Justice Shore had committed any reviewable errors in arriving at the conclusions on obviousness, anticipation and double patenting.

[25] Thereafter, Apotex appealed to the Supreme Court of Canada. On November 6, 2008, in *Apotex v Sanofi-Synthelabo Canada Inc.*, 2008 SCC 61, 69 CPR (4th) 251 (SCC *Plavix*), the Supreme Court of Canada, in a unanimous judgment written by Justice Rothstein, dismissed Apotex' appeal, again on the issues of obviousness, anticipation and double patenting. In its judgment, the Supreme Court of Canada modified the legal tests for the law of obviousness and anticipation. A review of the relevant legal principles will be considered later in this decision.

[26] In the context of the present case, Sanofi relied extensively on the decision of the Supreme Court of Canada in the NOC proceedings. However, the NOC proceedings and the fact conclusions they may have yielded are of limited assistance when, as here, the evidence adduced and the issues differ considerably from those presented in the course of the NOC proceedings. Indeed, unlike the

NOC proceedings, the present impeachment and infringement actions, at trial, involved *viva voce* testimony from nine (9) experts and fourteen (14) fact witnesses. Furthermore, these experts and fact witnesses were heard on a broader range of issues than those considered as part of the NOC proceedings. In particular, many were heard on the issue of sound prediction which, as seen later, is a central question before the Court. Yet the issue of sound prediction was not addressed as part of the NOC proceedings and there was accordingly no evidenciary record on that issue.

[27] On the issues of obviousness and anticipation, it is equally clear that the evidentiary record before the Federal Court of Canada, the Federal Court of Appeal, and the Supreme Court of Canada differed significantly from the record before the Court. Thus, whilst the Court recognizes that the legal principles and the questions of law decided by the Supreme Court of Canada in the NOC proceedings must necessarily be followed, the Court is not, however, bound by the factual findings made in the context of the NOC proceedings because the evidence is not necessarily the same. Hence, the NOC proceedings, whilst instructive, are not fact-determinative. As further noted by the Federal Court of Appeal, "factual findings are derived from the evidence that is before the court in the particular proceeding" and it is "incumbent upon the judge to arrive at his findings on the basis of the evidence that was before him" (*Ratiopharm Inc. v Pfizer Ltd.*, 2010 FCA 204, 87 CPR (4th) 185, at paras 25 and 26).

[28] It follows that NOC proceedings do not constitute *res judicata* (*Ratiopharm Inc. v Pfizer Ltd.*, 2009 FC 711, 76 CPR (4th) 241, at para 18; *Eli Lilly Canada Inc. v Novopharm Ltd.*, 2009 FC 235, 73 CPR (4th) 253). To put it another way, NOC proceedings are not the gospel.

IV Standing

A. *The Parties' Submissions*

(1) The Position of Apotex

[29] Apotex submits that one of the plaintiffs in this case, namely Bristol-Myers Squibb Sanofi Pharmaceuticals Holding Partnership (the Partnership), has no standing to bring the present action to the extent it relates to any acts of infringement alleged to have taken place prior to June 12, 2007, the date on which the Amendment to Clopidogrel Intellectual Property License and Supply Agreement (the Amended IP Agreement) was entered into between Sanofi and the Partnership. It is Apotex' position that the Partnership had no explicit licence prior to the Amended IP Agreement and that, furthermore, such an amendment cannot be applied to confer rights retroactively. Apotex argues that the Partnership is not the active entity that carries on in the foreign jurisdictions at issue and Apotex also argues that the Partnership does not operate in Canada. This, according to Apotex, bars the Partnership from seeking recovery in the form of damages in the circumstances.

(2) The Position of Sanofi

[30] In response, Sanofi asserts that, on the basis of its '777 Patent, there can be no question that it has standing to sue for infringement and obtain a remedy. As for the Partnership, Sanofi submits that it is an exclusive licensee under the '777 Patent and that the Partnership consequently has standing to sue for infringement and obtain a remedy as described in ss 55(1) of the *Patent Act*.

[31] More particularly, Sanofi argues that the Partnership is a "person claiming under" a patentee as stated in ss 55(1) of the *Patent Act* because the Partnership is assessing a right under the '777 Patent and that can be traced right back to the patentee. According to Sanofi, exclusive and non-

exclusive licensees, implied or oral, qualify as a "person claiming under" under a patentee (*Jay-Lor*, below).

[32] In this regard, Sanofi emphasizes that the Partnership has been given an explicit right to use and exploit the subject matter of the '777 Patent and clopidogrel bisulfate.

B. *Subsection 55(1) of the Patent Act – General Principles*

[33] The term "patentee" is defined in s 2 of the *Patent Act* to mean "the person for the time being entitled to the benefit of a patent". Because the patentee has monopoly over his patented invention, he may on this basis assign, licence or give a right to use his patent either exclusively or non-exclusively, in whole or in part. Significantly, ss 55(1) of the *Patent Act* provides a damages remedy and hence standing to claim damages not only to the patentee but also to "all persons claiming under the patentee". Subsection 55(1) provides as follows:

55. (1) A person who infringes a patent is liable to the patentee and to all persons claiming under him for all damages sustained by the patentee or by any such person, by reason of the infringement.	**55.** (1) Quiconque viole un brevet est responsable, envers le breveté et envers toute personne se réclamant du breveté, de tous dommages-intérêts que cette violation a fait subir au breveté ou à cette autre personne.

[34] The question of who qualifies as a person claiming under a patentee pursuant to ss 55(1) of the *Patent Act* has been analyzed numerous times by Canadian courts. In the 1972 case, *American Cyanamid Company v Novopharm Limited*, [1972] FC 739 (FCA), the Federal Court of Canada enlarged the meaning of "persons claiming under" when it held that a non-exclusive licensee of a patent is a person claiming under the patentee within the meaning of ss 55(1) of the *Patent Act*.

[35] Along the same lines, in *Armstrong Cork Canada Ltd. v Domco Industries Ltd.*, [1982] 1 SCR 907, 66 CPR (2d) 46, at p 912, the Supreme Court of Canada adopted the comments of Fry L.J. at p 470, in *Heap v Hartley*, (1889) 42 Ch D 461:

> […] An exclusive license is only a license in one sense; that is to say, the true nature of an exclusive license is this. It is a leave to do a thing, and a contract not to give leave to anybody else to do the same thing. But it confers like any other license, no interest or property in the thing. […]

[36] Another leading case in this regard is *Signalisation de Montréal Inc. v Services de Béton Universels Ltée* (FCA), [1993] 1 FC 341, 46 CPR (3d) 199, where the Federal Court of Appeal analyzed the issue of the rights of someone other than the patentee to maintain an action for infringement. In so doing, the Federal Court of Appeal considerably enlarged the pool of "persons claiming under the patentee". It held at pp 210-211 that:

> […] a person "claiming under" the patentee is a person who derives his rights to use the patented invention, at whatever degree, from the patentee. The right to use an invention is one the monopoly to which is conferred by a patent. When a breach of that right is asserted by a person who can trace his title in a direct line back to the patentee, that person is "claiming under" the patentee. It matters not by what technical means the acquisition of the right to use may have taken place. It may be a straightforward assignment or a licence. It may, as I have indicated, be a sale of an article embodying the invention. It may also be a lease thereof. What matters is that the claimant asserts a right in the monopoly and that the source of that right may be traced back to the patentee. […]

[37] More recently, Justice Snider in the case of *Laboratoires Servier v Apotex Inc*., 2008 FC 825, 67 CPR (4^{th}) 241, at para 77, found that "[t]he ability of a party to claim under a patentee does not necessarily require the existence of an express licence". She added that "[w]here no express

licence exists, each case will be determined on its facts to determine whether an implied licence or other right exists that gives rise to a claim "under the patentee".

[38] In addition, Justice Snider in *Servier*, above, at para 70, provided the following guidance:

> [70] The test for who qualifies as a person claiming under a patentee is not simply whether the patentee has consented to the person being joined as a plaintiff in an action; nor is it enough to demonstrate that two parties are related. In each case, the facts must demonstrate a credible and legally sufficient basis for claiming under a patentee (*Jay-Lor International Inc. v. Penta Farm Systems Ltd.*, (2007), 59 C.P.R. (4th) 228 at paras 31, 36 (F.C.) [Jay-Lor]).
>
> [Emphasis added]

[39] In light of these principles, the Court now turns to the BMS/Sanofi Partnership Agreements entered into between Sanofi and the Partnership.

C. *The BMS/Sanofi Partnership Agreements*

[40] The Partnership arose from the discovery of clopidogrel and irbesartan, two promising drugs. Because Sanofi had very little presence in the United States and Canada, it turned to Bristol-Myers Squibb (BMS) to create a partnership in order to commercialize the compounds on a worldwide basis. Sanofi and BMS accordingly entered into a Development Agreement in 1993, as well as a series of subsequent agreements including a Partnership Agreement, an Alliance Support Agreement (Territory A and B), a Product Know-How Licence Agreement and a Clopidogrel Intellectual Property License and Supply Agreement, all of which are dated January 1, 1997.

[41] In 2007, the parties decided to revise the initial Clopidogrel Intellectual Property License and Supply Agreement they had signed in 1997. This revised agreement was meant to address the needs of the alliance as the products were moving closer to commercialization and it included revisions to […] of the initial agreement listing the patent at issue. Thus, an Amendment to Clopidogrel Intellectual Property License and Supply Agreement was signed on December 6, 2007.

[42] The Court observes that contractual arrangements regarding the Partnership were structured around two territories, commonly referred to as Territory A and B. Territory B covers the United States, Canada, Mexico, South America, Australia and New Zealand, whereas Territory A includes Europe, Africa, the Middle East and Asia. Two territory partnerships were accordingly formed in order to manage central expenses, such as marketing, research and development and royalties, and to supply the finished product to the individual countries. At the country level, agreements either to co-promote or to co-market were also put in place.

[43] The Court further notes that the Product Know-How Licence Agreement confers rights to either party in the Partnership with regards to all technical data, information, material and other know-how that relates to the formulation of the products that are developed under the Development Agreement.

[44] As for the Clopidogrel Intellectual Property License and Supply Agreement (1997) as well as the Amended Agreement (2007), it grants an exclusive licence to the Partnership in the following terms:

> […] [omitted] .

[45] [omitted] .

[46] Against this background, the Court now turns to the evidence put before it in connection with the rights conferred to the Partnership.

D. *The Evidence before the Court*

[47] During the trial, Dr. Thierry Saugier, Vice-President Alliance and Partnership at Sanofi-Aventis, was called by Sanofi to testify as to the standing of the Partnership. Dr. Saugier testified that, since April 2006, he has managed group of alliances for Sanofi-Aventis, including the alliance referred to the Territory B Partnership and the Territory A Partnership.

[48] In particular, Dr. Saugier testified that, in order to structure the alliance, Sanofi granted an exclusive licence for clopidogrel to the Partnership, as can be seen in the Partnership Agreements which are still in effect today. The various agreements produced into evidence indeed support Dr. Saugier's oral testimony as to the rights granted thereunder.

[49] [omitted]:

Q. [omitted]?
A. [omitted].
Q. [omitted]?
A. [omitted].
Q. [omitted]?
A. [omitted].
Q. [omitted]?
A. [omitted].

[50] [omitted]:

Q. [omitted]?
A. [omitted].
Q. [omitted]?
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Q. [omitted]?
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Q. [omitted]?
A. [omitted].
Q. [omitted]?
A. [omitted].
Q. [omitted]?
A. [omitted].

[51] [omitted].

[52] [omitted].

[53] [omitted].

[54] [omitted]:

[omitted].

[55] The Court believes that such a list could not, on a practical point of view, be amended each time a development occurred in connection with products under research or in a process of a patent application. The terms and scope of the agreement at issue are such that […] must be interpreted to encompass newly developed compounds. To conclude otherwise would fly in the face of the very purpose of the Partnership Agreements, which was to allow the Partnership to carry out all activities

related to the development, manufacturing, sourcing and commercialization of clopidogrel in the specified territory known as Territory B, would otherwise be defeated.

[56] Finally, the Court recalls that counsel for Apotex questioned Dr. Saugier in connection with the absence of manufacturing facilities, employees and registered place of business in Canada in order to demonstrate the lack of standing. In light of the breadth of the Partnership Agreements, the Court finds this line of questioning to be of no assistance for the purposes of the standing issue.

E. *Conclusion on Standing*

[57] In sum, considering the broad meaning of "persons claiming under" a patentee as referred to under ss 55(1) of the *Patent Act*, and based on the Court's review of the Partnership Agreements and the testimony given in that regard, the Court finds that the Partnership has a "credible and legally sufficient basis" for claiming under a patentee in the circumstances. Indeed, the evidence clearly shows that the Partnership was granted an exclusive licence for clopidogrel products through the various Agreements as of 1997. It follows that the Partnership has standing to bring the action at issue for any infringement that it alleges to have occurred prior to December 6, 2007.

V Claims Construction

A. *General Principles*

[58] In a patent case such as the one at issue, the Court must first construe the claims of the patent in accordance with the principles of claims construction established by the caselaw (*Whirlpool Corp. v Camco Inc.*, 2000 SCC 67, 9 CPR (4th) 129; *Novopharm Ltd. v Janssen-Ortho*

Inc., 2007 FCA 217, 59 CPR (4th) 116; *Canada* (*Attorney General) v Amazon.com, Inc.*, 2011 FCA 328, [2011] FCJ No 1621).

[59] The Court observes that claims construction is a question of law and must be addressed with a purposive approach in order "to achieve fairness and predictability and to define the limits of the monopoly" (*Dimplex North America Ltd. v CFM Corp.*, 2006 FC 586, 54 CPR (4th) 435, at para 49, aff'd 2007 FCA 278, 60 CPR (4th) 277). In so doing, the Court is required to read the patent claims with "a mind willing to understand" (*Whirlpool*, above).

[60] Conceptually, the claims construction analysis focuses on what a hypothetical person of ordinary skill in the art (POSITA) would have understood the patent to claim (*Whirlpool*, above, at paras 45, 53). This, in turn, requires that the Court first determine the requisite skills and expertise for the POSITA (*Aventis Pharma Inc. v Apotex Inc.*, 2005 FC 1283, 43 CPR (4th) 161; *Apotex Inc. v Syntex Pharmaceuticals International Ltd*, [1999] FCJ No 548, 166 FTR 161, at para 38, (QL) (FCTD)).

[61] Furthermore, as the patent should be read as a whole, the claims should be read in light of the description in the specification, assisted by experts as to the meaning of technical terms used therein (*Shire Biochem Inc. v Canada (Minister of Health)*, 2008 FC 538, 328 FTR 123, at para 22; *Whirlpool*, above, at para 45).

[62] The Court further recalls that, because the '777 Patent was issued under the old *Patent Act*, all claims are to be construed as of the date the patent was granted and issued (*Pfizer Canada Inc. v*

Canada (Minister of Health), 2005 FC 1725, 285 FTR 1, at para 36). In the case of the ‘777 Patent, the relevant date is August 22, 1995.

[63] With these general principles of claims construction in mind, the Court now turns to its assessment of the POSITA.

B. *The Hypothetical Person of Ordinary Skill in the Art (POSITA)*

[64] In assessing the hypothetical POSITA, the Court must define the person or group to whom the ‘777 Patent is addressed. This person is obviously not a real person. As explained by Justice Hughes in *Merck & Co v Pharmascience Inc*., 2010 FC 510, 85 CPR (4^{th}) 179, at para 42: “[T]hat person is to be unimaginative, but that does not mean that the person is slow-witted or graduated (if at all) at the bottom of the class. Nor is the person the gold medalist who graduated at the top of the class. That person is the average person in the group. Just as a “reasonable man” is expected to be reasonable, the POSITA is expected to possess the ordinary skill in the art”.

[65] The Supreme Court of Canada considered such a person in *Whirlpool*, above, at para 74, where Justice Binnie for the Court wrote that the POSITA refers to the hypothetical “ordinary worker” who is reasonably diligent in keeping up with advances in the field to which the patent relates.

[66] In *Merck & Co v Pharmascience Inc.*, above, at para 35, Justice Hughes further referred to submissions made by the Canadian Group of AIPPI (Association internationale pour la Protection

de la Propriété intellectuelle) and to a summary under Canadian law as to what a POSITA is understood to be:

> 35. …
>
> Q.213 Summary
>
> In Canada, the "person of ordinary skill in the art" is the hypothetical person to whom the patent is addressed. This may be a single individual or a group representing different disciplines, depending on the nature of the invention. The person of ordinary skill in the art is deemed to be unimaginative and uninventive, but at the same time is understood to have an ordinary level of competence and knowledge incidental the field to which the patent relates (i.e. the common general knowledge) and to be reasonably diligent in keeping up with advances. The common general knowledge is that knowledge generally known by persons skilled in the relevant art at the relevant time. Accordingly, it can include knowledge passed amongst people in the field, including information that is not in published form. Likewise, not everything that has been published is within the common general knowledge.

Evidence Adduced by the Experts on the POSITA

[67] The Court heard from numerous experts on behalf of both Apotex and Sanofi in connection with the POSITA, as set forth next.

Apotex' Experts

[68] Dr. Hirsh stated that the '777 Patent is addressed to persons skilled in clinical medicine/haematology, biochemistry, chemistry, pharmacology, toxicology, and pharmacy.

[69] Dr. Adger opined that the '777 Patent is addressed to a person with skills in chemistry, haematology, toxicology, pharmacology and pharmaceutical formulations. In regard to the issues of chemistry, the person would have post-graduate level training in organic chemistry with special

focus in synthetic or medicinal chemistry and/or a combination thereof. Such a person would also have several years of experience in synthesizing organic pharmaceutical compounds, including resolving racemic drugs or otherwise making single enantiomer medicines. This person would understand basic concepts of stereochemistry, would be generally familiar with techniques for the analysis and separation of enantiomers and would have familiarity with enantiomeric pharmaceutical drugs.

[70] Dr. Levy submitted that the '777 Patent covers areas of chemistry, medicine, haematology and platelets, pharmacology, toxicology and pharmaceutical formulation. Regarding areas of pharmacology, the person the '777 Patent addresses is a Ph.D. level pharmacologist with at least several years of working as a pharmacologist.

[71] Dr. Sanders indicated that the patent addresses issues of chemistry, pharmacology, mechanisms of platelet aggregation and thrombosis, toxicology, pharmaceutical formulation, and medicine. He further opined that the patent engages a variety of disciplines, one of which is toxicology. With regard to toxicology, the person to whom the patent is addressed is a trained toxicologist having a Ph.D. in pharmacology or toxicology together with two or three years of experience in the toxicology of pharmaceutical products. The person could also have a Master's degree in these fields with about five years of practical experience or a bachelor's degree in these fields with approximately ten years of experience.

Sanofi's Experts

[72] Dr. Byrn stated that the '777 Patent is primarily addressed to an ordinary person working in the synthesis or formulation of pharmaceutical compounds. Such a person would have at least a bachelor's degree in chemistry or a related discipline and several years of experience working in a pharmaceutical laboratory synthesizing or formulating pharmaceutical compounds.

[73] Dr. Rodricks agreed that the '777 Patent is directed to many different areas including chemistry, toxicology, pharmacology, salts and pharmaceutical compositions. His understanding is that a person skilled in the art as it relates to the toxicology aspects would have an advanced degree in toxicology or pharmacology, or in biochemistry, or a related subject with additional specific training and experience in the area of toxicology and drug safety, including the evaluation and interpretation of toxicology data.

[74] Dr. Davies opined that a person of ordinary skill in the art is a pharmaceutical chemist having a bachelor's or doctoral degree in chemistry or a related discipline and several years of experience working in a pharmaceutical laboratory synthesizing drug compounds. The understanding of the invention of the '777 Patent is the knowledge and experience of stereochemistry, chiral separation, and drug discovery are crucial to the understanding of the invention of the '777 Patent. Therefore, a pharmaceutical chemist with experience in stereochemistry has this background. Dr. Davies disagreed that toxicologists and medical doctors are persons to whom the '777 Patent is addressed.

[75] Dr. Shebuski indicated that the ‘777 Patent is primarily directed to a pharmaceutical chemist, but also to a pharmacologist and toxicologist to the extent they are asked by the pharmaceutical chemist to conduct testing relating to the compound that the chemist has made.

The Court's Findings on the POSITA

[76] As gleaned from the above, Apotex advances that the POSITA includes not only a pharmaceutical chemist but also a toxicologist, haematologist and medical doctor. Sanofi, on the other hand, argues that the POSITA is a pharmaceutical chemist.

[77] While the Court agrees with Sanofi and Dr. Davies that the ‘777 Patent is addressed to a pharmaceutical chemist because experience in stereochemistry, chiral separation and drug discovery is key to understanding the ‘777 Patent, the Court cannot agree to an interpretation of the POSITA limited to a pharmaceutical chemist. This would amount to providing the pharmaceutical chemist with the “loudest voice” (*Merck and Co v Pharmascience Inc*., above). The Court considers that there is more to the understanding of the ‘777 Patent than possessing merely the skill of pharmaceutical chemistry. The ‘777 Patent contains a variety of aspects as emphasized by both Dr. Levy for Apotex and Dr. Rodricks for Sanofi. In that context, the POSITA has to be approached as a team of persons as opposed to a single person with all the skills.

[78] More particularly, the ‘777 Patent addresses identity and chemical structure of the enantiomer known as the dextro-rotatory enantiomer of methyl alpha-5 (4,5,6,7-tetrahydro (3,2-C) thieno pyridyl) (2-chlorophenyl)-acetate and its racemate and the levo-rotatory enantiomer. The patent discusses a method for isolating the two enantiomers from the racemic mixture, methods of

forming the pharmaceutically-acceptable salts of the two enantiomers and methods of preparing pharmaceutical compositions.

[79] The ‘777 Patent also addresses comparative pharmacological and toxicological properties of the two enantiomers and the racemate. It further makes reference to their respective ability to be used as medicines in pharmaceutical compositions of particular dosage strengths with respect to the mechanisms of arterial and venous thrombosis that are to be used in treatment of platelet disorders due to extracorporeal blood circuits and the complications of atheroma.

[80] The Court accordingly concludes that the hypothetical person skilled in the art (POSITA) in the case at bar consists of a number of skilled individuals; holding a Ph.D in pharmaceutical chemistry; with several years of experience working in the fields of pharmacology and toxicology; and having good general knowledge of haematology and medicine.

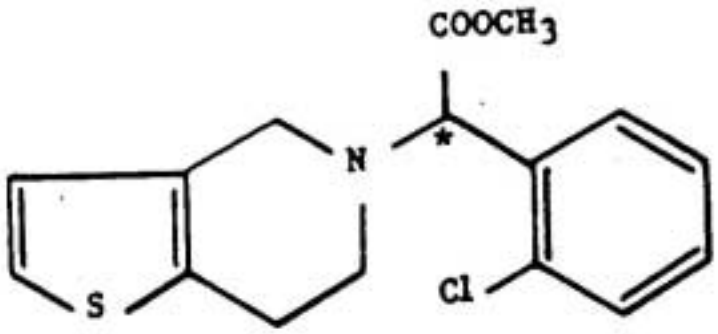
C. *The Patent Specification*

[81] Having established the POSITA, the Court must now consider the patent specification at issue.

[82] The Court notes that the ‘777 Patent is a selection patent. It begins, at page 1, with a general statement of the invention relating to the compound, its process, its preparation and its composition as follows:

> The present invention relates to the dextro-rotatory enantiomer of methyl alpha-5 (4,5,6,7-tetrahydro (3,2-c) thieno pyridyl) (2-chorophenyl)-acetate, a process for its preparation and pharmaceutical compositions containing it.

[83] The patent further specifies that the compound of the invention contains a pyridine ring, a phenyl ring, a chiral center and an H-bonding group. The compound of the invention corresponds to the following formula:



(I)

[84] At page 1 of the Patent, at line 25, the inventors distinguish their invention from the prior art and further specify at line 29 that the invention also relates to salts:

> In an unexpected manner only the dextro-rotatory enantiomer I_d exhibits a platelet aggregation inhibiting activity, the levo-rotatory enantiomer I_l being inactive. Moreover, the inactive levo-rotatary enantiomer I_l is the less well tolerated of the two enantiomers. The invention also relates to the addition salts of the compounds of formula (I_d) with pharmaceutically acceptable mineral or organic acids.

[85] At page 2 of the Patent, the inventors begin a discussion on salts. They mention that some of the salts of the dextro-rotatory enantiomer I_d are sometimes difficult to handle on an industrial scale because they precipitate in an amorphous form and/or they are hygroscopic. However, at page 2, at line 10, it is said that salts have been found that crystallize easily, are not hygroscopic and have good water solubility:

> Among the mineral and organic acid salts of the dextro-rotatory isomer of the compound of Formula (I_d) salts have been found which crystallize easily, are not hygroscopic and are sufficiently water-soluble as to make their use as active medicinal principles particularly advantageous.

[86] Specifically, the inventors explain that "[t]he present invention thus relates more particularly to the hydrogen sulfate, the taurocholate and the hydrobromide of the dextro-rotatory enantiomer of methyl alpha-5 (4,5,6,7-tetrahydro (3,2-c) thieno pyridyl) (2-chlorophenyl)-acetate".

[87] The Court notes that beginning at the bottom of page 7 through to page 11, the inventors go on to provide examples to the reader to illustrate the invention.

[88] Thereafter, at page 12, the Patent discloses the results of a pharmacological study and sets forth another advantage of the invention:

> A description will now be given of the results of this study which demonstrates another advantage of the invention, namely that the salts of the dextro-rotatory isomer have a better therapeutic index than the salt of the racemic mixture; in fact, the levo-rotatory isomer exhibits almost no platelet aggregation inhibiting activity and its toxicity is markedly higher than that of its dextro-rotatory homologue.

[89] The result of the pharmacological study is described in four (4) distinct Tables:

- Table I, at page 14, relates to platelet aggregation inhibiting activity assay using ADP. According to the patent, the data "demonstrate that the levo-rotatory isomer is inactive and that the dextro-rotatory isomer [clopidogrel] is at least as active as the racemate".

- Table II, at page 16, relates to platelet aggregation inhibiting activity assay using collagen, the results "demonstrate again that only the dextro-rotatory isomer [clopidogrel] is active whereas the salts have comparable activities".

- Table III, at page 18, relates to the antithrombotic test. According to the patent, the results "show that the levo-rotatory isomer is inactive in this test, in contrast to the dextro-rotatory isomer [clopidogrel] and the racemate".

- Lastly, Table IV, at page 19, relates to the LD_{50} test. According to the patent, the results "show on the one hand that the toxicity of the racemic mixture is similar to that of the levo-rotatory isomer whereas the dextro-rotatory isomer [clopidogrel] is markedly less toxic, and, on the other hand, that the toxicity depends on the nature of the acid used to form the salt".

[90] Following the four (4) above-described tables, the '777 Patent at pages 12 to 19 sets out three (3) different tests performed on female rats:

> Test no. 1: the compounds were administered to groups of five female rats of the CD-COBS strain and then blood samples were taken from the animals after the compounds have been metabolized in the rats for two hours. Platelet rich plasma was then isolated and aggregation is induced either with ADP (the '777 Patent, Table 1) or collagen of type 1 (the '777 Patent, Table II). Aggregation of the platelets was then monitored and a curve is generated to represent a change in optical density. This type of test is known as an *ex vivo* test because although compounds were administered to animals and blood removed, the test was performed outside of living animals. The results of the tests are reported in Tables I and II.
>
> Test no. 2: this test was inspired by the test developed by Kumada in 1980 (*Kumada et al*. "Experimental model of venous thrombosis in rats and effect of some agents" 1980, Thrombosis Research 18; 189-203). It is an *in vivo* test and was performed by inserting a steel wire into the inferior vena cava of a rat. After a period of time a thrombosis develops on the wire and the weight of the thrombus is measured in untreated rats and those treated with the test compound. The difference in weight of thrombosis formed with and without the administration of various drugs is used as a measure of the antithrombotic of the test compound. It is also known as the AV/Shunt model. The results of this test are presented in Table III.
>
> Test no. 3: The third test was the LD_{50} test. This test is an acute toxicity test where the measured endpoint of the experiment is death

> in 50% of the animals treated. The lethality is a response that occurs at very high doses with a single administration. The results are in Table IV.

[91] Then at page 20 at line 4, the Patent explains how the invention can be used:

> The medicine of the invention can be made available for oral administration in the form of tablets, sugar-coated tablets, capsules, drops, granules or a syrup. It can also be made available for rectal administration in the form of suppositories or for parenteral administration in the form of an injectable solution.

[92] Further, at page 20 at lines 15 to 35, the Patent makes reference to some pharmaceutical formulations of the medicine of the invention for tablets, sugar-coated tablets, capsules, injectable solution and suppositories.

[93] Finally, at page 21, on which there is a sole paragraph, reference is made to medicine of the invention as follows:

> On account of its interesting inhibitory properties towards platelet aggregation and its interference in the mechanism of formation of arterial and venous thromboses, the medicine of the invention can be usefully administered in the treatment and prevention of platelet disorders due to extracorporeal blood circuits or the consequence of complications in atheroma.

[94] The Court now turns to the Patent claims at issue.

D. *The Claims at Issue*

[95] By way of a preliminary observation, the Court notes that the ‘777 Patent has eleven (11) claims and they are set forth at pages 22 and 23 thereof. These claims can be grouped as follows:

- Claims 1 to 5 relate to clopidogrel and its salts;
- Claims 6 to 9 relate to the process of making clopidogrel;
- Claims 10 and 11 relate to the pharmaceutical compositions.

The Court observes that there are a number of areas of disagreement between Apotex and Sanofi which are the following:

- The Purity of Claims 1, 3, 10, 11;
- The Limitations of Claims 6 to 9;
- What is the meaning of "Medicine of the Invention";
- Page 21 of the '777 Patent; and
- The Invention described in the '777 Patent.

E. *Claims 1, 3, 10 and 11*

[96] The only relevant issue with respect to the construction of Claims 1, 3, 10 and 11 concerns the degree of enantiomeric purity of the clopidogrel referred to in these claims. Apotex submits that the disclosure of the racemate discloses clopidogrel that is 50% pure. The '777 Patent contains no purity limitation.

[97] The '777 Patent at page 7 discusses the determination of the enantiomer (optical) purity of the dextro-enantiomer and the levo-enantiomer. It further states that, under the conditions described, the optical purity is at least equal to 96% for the dextro-rotatory enantiomer and at least equal to 98% for the levo-rotatory enantiomer.

[98] From this observation, the experts for both parties (Dr. Byrn, Dr. Hirsh and Dr. Adger) agreed that the purity of the clopidogrel claimed in the '777 Patent - although not 100% pure - is "substantially pure".

[99] Furthermore, Dr. Hirsh testified that the number of at least equal to 96% for the dextro-rotatory enantiomer, and 98% for the levo-rotatory enantiomer and with respect to the optical purity is relative to the limit of detection.

[100] On this basis, and given that the independent claim has been construed as "substantially pure", the Court concludes that the dependent claims should also be construed as "substantially pure".

[101] Hence, the Court finds that a POSITA would conclude that Claim 3 encompasses "substantially pure" hydrogen sulfate salt of clopidogrel.

F. *The Limitations of Claims 6 to 9*

[102] As mentioned above, Claim 6 relates to the general process of making clopidogrel and its pharmaceutically acceptable salts. This general process can be summarized as follows:

- formation of a salt of the racemate with an optically active acid in a solvent;
- performing repeated recrystallizations of the salt until a product of constant optical rotatory power is obtained;
- liberation of the salt by a base; and, if desired;
- formation of a salt with a pharmaceutically acceptable acid.

[103] Apotex' argument in this regard is articulated as follows:

> Claim 6 claims a general process, the Pasteur method referred to by many experts as the classic method, starting with the racemic mixture. Claim 7, then, narrows it where it is the levo-rotatory camphor-10-sulphonic acid that is used, a standard acid. Claim 8 then narrows Claim 6 to use the solvent acetone. And Claim 9 deals with comprising the formation of a salt in acetone. In sum, Apotex' view is that claims should not just be read by themselves,

> but in conjunction with the disclosure, because the claims on their own sometimes fail to tell enough.

[104] In this case, the Court is not persuaded by Apotex' argument.

[105] Rather, a claim comparison and differentiation indicates that Claim 6 of the '777 Patent should be read, compared and contrasted with Claims 7 to 9. Indeed, Claims 7 to 9 also relate to the making of clopidogrel and its pharmaceutically acceptable salts. A reading of Claims 7 to 9 confirms that they include specifications with respect to the solvent and optically active acid used. More particularly, Claim 7 relates to the process as described in Claim 6, but the optically active acid is specified as being levo-rotatory camphor-10-sulfonic acid. Claim 8 relates to the process as described in Claim 6, but specifies the solvent used in the recrystallization steps as acetone. Claim 9 relates to the process as described in Claim 6, but specifies the solvent used in the formation of a salt as acetone.

[106] Apotex nonetheless appears to allege that Claim 6 is limited to the acid and solvents discussed in Claims 7 to 9. The Court does not agree.

[107] The Court recalls that the Supreme Court of Canada in *Whirlpool*, above, at para 49, emphasized that patent claims "must be read with a mind willing to understand". Reading Claim 6, as proposed by Apotex, disturbs the flow and distorts the logic of the process claims (*i.e.* Claims 6 to 9) and this runs counter to the Supreme Court of Canada's interpretative guidance. Indeed, what would be the purpose and the relevance of the more specific Claims 7 to 9 if the more general process Claim 6 was limited in the manner suggested by Apotex? The Court also notes that, at page

2, the ‘777 Patent mentions that the levo-rotatory camphor-10-sulfonic acid is “advantageously used” and that acetone is “ideally suited”. This wording implies that other acids and solvents could be used as well. Hence, bearing in mind the guiding principles enunciated in *Whirlpool*, above, and, upon reading Claims 6 to 9, the Court finds that a person skilled in the art would construe Claim 6 as not limiting the “optically active acid” to levo-rotatory (*R*)-camphor-10-sulfonic acid (Claim 7) and not limiting the solvent to a particular one. In sum, Claim 6 includes the use of optically active acids and solvents that result in the preparation of substantially pure clopidogrel and its pharmaceutically acceptable salts following the process described in Claim 6.

G. *What is the Meaning of “Medicine of the Invention” ?*

[108] The Court recalls that Apotex argues that the ‘777 Patent addresses matters of medicine, whereas Sanofi maintains that the ‘777 Patent refers to clopidogrel as a compound rather than a medicine.

[109] Where there are technical terms in a patent, the Court is assisted by experts as to the meaning of such terms. The term the “medicine of the invention” as referred to in the ‘777 Patent is one such technical phrase that must be interpreted by the Court (*Shire Biochem Inc.*, above, at para 22; *Whirlpool*, above, at para 45). Indeed, the meaning of the phrase “medicine of the invention” informs the promise of the patent and must be ascertained at this stage of the analysis before the promise of the patent can be determined.

[110] Central to this debate are also the meaning and use of the phrase “medicine of the invention” as well as “compound of the invention”.

[111] In order to address this issue, the Court must look to the wording of the ‘777 Patent and weigh the experts’ opinions.

[112] First, the ‘777 Patent. The patent in referring to clopidogrel uses the terms “compound of the invention”, “derivative of the invention” and “medicine of the invention”.

[113] At page 13, the ‘777 Patent, in the context of its discussion on salts, states the following:

> Among the mineral and organic acids salts of the dextro-rotatory isomer of the compound of Formula (Id) salts have been found which crystallize easily, are not hygroscopic and are sufficiently water-soluble as to make their use as active medicinal principles particularly advantageous.
>
> [Emphasis added]

[114] Also, at page 20, the ‘777 Patent specifies that the medicine of the invention “can be made available for oral administration in the form of tablets, sugar-coated tablets ...”. The patent further specifies the unit doses for the compositions and the daily doses to be administered to patients to treat the disorders addressed by the patent.

[115] Second, the experts. The experts opined on the significance of the meaning of the terms the “medicine of the invention”. For instance, in his report, at para 74, Dr. Davies stated that “[t]he invention of the ‘777 Patent improved PCR 4099 molecule by removing the enantiomer that contributed toxicity but no activity, thus providing a safer, more effective drug”. (Emphasis added)

[116] The exchange between counsel for Apotex and Dr. Shebuski is also instructive as to whether the "medicine of the invention" is clopidogrel as described in the '777 Patent (Shebuski, cross T5281-5294):

> Q. Dr. Shebuski, you will agree with me that clopidogrel is a medicine?
> A. Yes, sir.
> Q. Thank you. I want to ask you about the '777 Patent. Could you open it?
> A. I have it open, sir.
> Q. Perfect. You were anticipating my next move.
> A. I'm on page 21.
> Q. If you go to page 23 with me, I want to ask you about claims 10 and 11. You talk about those in your paragraphs 41 and 42. Claim 10 begins with the words "A pharmaceutical composition." Am I correct that a skilled person reading this would understand that pharmaceutical refers to a drug or a medicine?
> A. Yes, sir. Properly formulated.
> Q. Properly formulated. And it's a drug or medicine that's intended to be given to people?
> A. It could be given to animals, as well, as a veterinary product.
> Q. Okay. You may have just anticipated this. The composition is the formulation or the thing that's going to deliver the medicine to the patient?
> A. That's correct. Composition could include the salt or the carrier or other excipients that were involved with the active ingredient, which we call the API or active pharmaceutical ingredient.
> Q. If we go forward, we're told that the pharmaceutical composition comprises an effective amount of a compound according to claim 1. I want to ask you about the compound according to claim 1. That would be understood to be a reference to clopidogrel and its pharmaceutically acceptable salts, which are described in claim 1. Correct?
> A. Yes, sir.
> Q. When it says "an effective amount of clopidogrel and its pharmaceutically acceptable salts," I take it the words "effective amount" reveal the concept of an amount that's sufficient to treat whatever it is you're wanting to treat with the composition?
> A. Well, my analysis of it is slightly different. The effective amount is the amount that inhibits platelet aggression, which relates to the utility of this patent.
> Q. What amount of platelet aggregation? In the abstract? Any amount?
> A. Well, an effective amount. As I mentioned earlier in my testimony, we look at inhibition levels of 50 percent or greater as an effective amount.
> Q. Where is that said in the patent?
> A. It's not said in the patent. That's my own conjecture, sir.

> Q. Conjecture. Okay. I'm going to suggest to you that, given that we are talking about a pharmaceutical composition, when it says, "Such a composition comprising an effective amount of clopidogrel and its pharmaceutically acceptable salts," you have already told me clopidogrel is a medicine, so I'm going to suggest to you it's an effective amount of the medicine to be able to do what the medicine is supposed to do. Do you agree with that?
>
> A. I have no basic disagreement with that.
>
> [Emphasis added]

[117] Dr. Hirsh was also inclined to state that the "medicine of the invention" relates to clopidogrel and Dr. Levy was of the view that a compound, when active, can be a medicine even before it is formulated.

[118] Thus, on the basis of the terms used in the '777 Patent, as well as the experts' opinion on behalf of both Sanofi and Apotex, the Court agrees with Apotex and concludes that matters of medicine in the '777 Patent are "inescapable". The Court accordingly finds that the "medicine of the invention", as referred to in the '777 Patent, relates to clopidogrel.

H. *Page 21 of the '777 Patent*

[119] Another issue in dispute between the parties is the meaning of page 21 of the '777 Patent, which is an issue the Court needs to address as it will inform the promise of the Patent.

[120] Page 21 of the '777 Patent contains one paragraph and it reads as follows:

> On account of its interesting inhibitory properties towards platelet aggregation and its interference in the mechanism of formation of arterial and venous thromboses, the medicine of the invention can be usefully administered in the treatment and prevention of platelet disorders due to extracorporeal blood circuits or the consequence of complications in atheroma.

[121] The positions of the parties regarding the above could not be further apart. Indeed, Apotex' position is that page 21 of the '777 Patent guarantees treatment in humans whereas Sanofi's position is that page 21 of the '777 Patent does not in any way make reference to treatment in humans or, if it does, only to the "potential" for use in humans.

[122] The expert evidence on this issue has not convinced the Court that the '777 Patent guarantees treatment of arterial and venous thrombosis as alleged by Apotex. The Court is equally unconvinced that the '777 Patent may refer to the "potential" for use in humans as alleged by Sanofi. A review of the testimony of the experts simply does not support either of the opposite views expressed by the parties at trial.

[123] Whilst the '777 Patent does not refer to a guarantee, it does refer to more than a remote "potential" in humans. Unable to accept either of the two extreme interpretations of page 21 urged by the parties, the Court finds that the '777 Patent makes reference to use in humans.

[124] The Court recalls that Dr. Hirsh, an expert for Apotex, in cross-examination, could not firmly conclude that page 21 of the '777 Patent promised treatment of venous thrombosis (Hirsh, T671-674):

> Q. And to the extent your report says that the patent promises treatment of venous thrombosis, that's a bit of an inflation?
> A. Could I see where I said that?
> Q. Well, yes, sure. I mean if you don't say it in your report, that's fine. But let me find it.
> Well, for instance in paragraph 188 you are referring to ticlopidine and the racemate, but you do use the phrase prevention and treatment in

venous thrombosis. That's paragraph 188, right at the bottom of the page, the top of the next page, page 64.

A. Yes, but that's a slightly different context isn't it.

Q. And that's why, but when I read that I was saying, "well, why are you talking about treatment of venous thrombosis if the triple 7 doesn't promise that"?

A. It's just a statement of fact.

Q. Fair enough.

A. It's a statement of fact, but I didn't say it promised it. I was aware it was a mechanism. The only reason I would be interested in the mechanism would be if it had any utility, but that's implied rather than explicit.

[Emphasis added]

[125] However, Dr. Hirsh further testified that clopidogrel has a role in the mechanism of the formation of arterial and venous thrombosis (Hirsh, T682):

Q. Let's turn to the mechanism of formation of arterial and venous thrombosis which are the words that do appear.

A. Yes.

Q. I think you have already testified that platelets are involved in the formation of arterial and to a lesser degree venous thrombosis?

A. Were they--yes, I have.

Q. So if you have an inhibitor of platelet aggregation, its role in the mechanism of the formation of arterial and venous thrombosis is to prevent aggregation?

A. Correct.

Q. And that's all it's saying here?

A. I see, um hmm.

[Emphasis added]

[126] Dr. Davies, on behalf of Sanofi, in his report at para 246, opined, with respect to page 21 of the '777 Patent, that it was not to be understood as a guarantee for use in humans:

> Consequently, when I read the entire paragraph on page 21, what is being said is that the improvement in activity and toxicity (based on animal testing) means that the medicine of the invention (i.e. if and when the compound is used as medicine) can (i.e. has potential) to be used for treatment. This is exactly what a skilled pharmaceutical chemist would take from the information in the patent. It would not be understood to be a promise of clinical approval, or a guarantee of use in humans.

[127] During the evidentiary phase of the trial, Dr. Davies elaborated on the above (T4425-4426):

> Q. In 246, you give your understanding of the last part of that paragraph on page 21. What is your understanding that you're telling us there?
> A. What I'm saying there is, if you read the whole paragraph, the utility, from the first part of the paragraph, is the platelet aggregation inhibition. The rest of the paragraph suggests a potential use perhaps of that platelet inhibition.
> Q. Thank you. In paragraph 247, you refer to the claims and you make a comment that there's no use for treatment in humans. I think we're all aware of that, but you refer then to claims 10 and 11?
> A. Yes.
> Q. What are you telling us in connection with claims 10 and 11?
> A. Claims 10 and 11 talk about pharmaceutical composition involving the clopidogrel as the constituent of that composition, but don't imply any use of that in humans. It could be in animals, for example.
>
> [Emphasis added]

[128] In light of its earlier finding with respect to the meaning of the phrase "medicine of the invention", the Court cannot accept such a restrictive reading down of the meaning of page 21 of the '777 Patent, as suggested by Dr. Davies. The Court refers *mutatis mutandis* to the comments expressed by Justice Snider in *Sanofi-Aventis Canada Inc. v Apotex Inc*,, 2009 FC 676, 77 CPR (4th) 99, (*Ramipril*), (decision affirmed on November 2, 2011 by the Federal Court of Appeal), at para 128:

> [128] This passage demonstrates that Dr. Bartlett has not construed the claims in light of the promised utility; rather he has modified or read down the promise of the patent to suit his understanding of the claims. I cannot accept this reasoning. Such an approach to the question of the promise of the patent excuses the inventors from any requirement of precision in their claims or in the patent specification. If a patentee promises a particular result, he should be held to that promise. In expressing this view, I am not requiring commercial success or a certain level of commercial development to have taken place. …

[129] In the present circumstances, the language used at page 21 of the ‘777 Patent is not clear as to whether or not it guarantees that clopidogrel will “prevent” or “stop” the “mechanism of formation of arterial and venous thromboses”. There is simply no explicit wording to this effect.

[130] Yet, the wording in the ‘777 Patent does not make it clear that the purpose is not for humans and the Court is not convinced that page 21 of the ‘777 Patent merely describes a “potential” use for humans.

[131] In sum, the Court finds that Apotex is looking to inflate the meaning of page 21 of the ‘777 Patent, whereas Sanofi is urging that it be read down. It is difficult if not impossible to conclude that page 21 of the ‘777 Patent clearly makes reference to a guaranteed treatment in humans. It is equally difficult to find that page 21 of the ‘777 Patent does not in any way make reference to treatment in humans. The Court is thus not prepared to conclude that page 21 of the ‘777 Patent is stripped of all reference to humans as advanced by Sanofi. How could this be when the diseases referred to at page 21 of the ‘777 Patent are not in animals but in humans (Hirsh, T391-393)? It necessarily means that it has a human purpose of some kind.

[132] The Court accordingly concludes that the reference at page 21 of the ‘777 Patent that “the medicine of the invention can be usefully administered in the treatment and prevention of platelet disorders due to extracorporeal blood circuits or the consequence of complications in atheroma” confirms that clopidogrel on account of its properties, whilst not a guarantee, promises more than a mere potential: it can be used in the treatment of certain human thrombotic diseases.

I. *The Invention described in the '777 Patent*

[133] The Court observes that there is no issue between the parties with respect to the inventive concept of the '777 Patent. The inventive concept was described as follows in the Supreme Court of Canada of the '777 Patent in the *Plavix* decision, at para 78:

> [78] In the present case, it is apparent that the inventive concept of the claims in the '777 patent is a compound useful in inhibiting platelet aggregation which has greater therapeutic effect and less toxicity than the other compounds of the '875 patent and the methods for obtaining that compound.

[134] The '777 Patent is a selection patent (*i.e.* as stated in *Plavix* it is "one whose subject matter (compounds) is a fraction of a larger known class of compounds which was the subject matter of a prior patent"). Thus the Court must now address the question of how the inventive concept relates to the invention. More particularly, the question is the following: Do the salts and the advantages form part of the invention? Sanofi argues that the salts and the advantages could only relate to Claim 3 and the bisulfate salt, whereas Apotex maintains that the salts and their advantages related to the invention described in the '777 Patent.

[135] In *Olanzapine*, below, at para 78, the Federal Court of Appeal provided helpful guidance with respect to selection patents in the following:

> [78] With respect to selection patents, the inventiveness lies in the making of the selected compound, coupled with its advantage or advantages, over the genus patent. The selection patent must do more, in the sense of providing an advantage or avoiding a disadvantage, than the genus patent. The advantage or the nature of the characteristic possessed by the selection must be stated in the specification in clear terms…

[136] Thus, whilst in the context of a selection patent, the advantages will often necessarily form part of the invention, other scenarios remain possible. For example, the Court could hypothetically envisage a selection patent relating to the invention of a new process. In such a case, the new process could be found to be a second invention independent of the advantages stated in the selection patent. However, this is not the case with the '777 Patent because it relates to only one invention as discussed later in these reasons:

- Firstly, the process of splitting the racemate (PCR 4099) into two distinct enantiomers was not achieved through a new process. The process leading to the two enantiomers (the dextro-rotatory and the levo-rotatory) was performed following the Pasteur method.

- Secondly, a reading of the '777 Patent confirms that there is only one invention (pp 1 and 25) :

  > At page 1 the patent states that "[t]he present invention relates to the dextro-rotatory enantiomer of methyl alpha-5 (4,5,6,7-tetrahydro (3,2-c) thieno pyridyl) (2-chorophenyl)-acetate, a process for its preparation and pharmaceutical compositions containing it".
  >
  > In an unexpected manner only the dextro-rotatory enantiomer I_1 exhibits a platelet aggregation inhibiting activity, the levo-rotatory enantiomer I_1 being active. Moreover, the inactive levo-rotatory enantiomer I_1 is the less well tolerated of the two enantiomers.
  >
  > [Emphasis added]

[137] Significantly, the '777 Patent at page 1 at line 29 refers to the invention mentioned and further specifies that: "the invention also relates to the addition of salts of the compound of formula (I_1) with pharmaceutically acceptable mineral or organic acids". Furthermore, the '777 Patent states at page 2 that the advantages provided by these salts include the characteristics of crystallizing easily, of not being hygroscopic and, being sufficiently water-soluble.

[138] The Court thus concludes from the wording of the ‘777 Patent that there is only one invention and the invention relates to salts of the compound and its advantages.

[139] Therefore, the Court cannot agree with Sanofi’s contention that “there is one invention with different aspects, but each claim has to be considered separately within the invention”. The Court equally rejects the suggestion that the salts and the advantages may be peripheral to the invention.

[140] In summary, the ‘777 Patent relates to one invention and that can be described as a compound which is useful in inhibiting platelet aggregation, has greater therapeutic effect and less toxicity than the other compounds of the ‘875 Patent, has the advantages of the salts (crystallize easily, not hygroscopic and sufficiently water-soluble) and the methods for obtaining that compound.

J. *Construction of the Promise of the Patent*

(1) General Principles

[141] The promise of the patent is a question of law for the Court to decide, aided by the experts and considered through the eyes of the POSITA, as reiterated by the Federal Court of Appeal in *Eli Lilly Canada Inc. v Novopharm Limited*, 2010 FCA 197, 85 CPR (4th) 413, at para 80:

> [80] The promise of the patent must be ascertained. Like claims construction, the promise of the patent is a question of law. Generally, it is an exercise that requires the assistance of expert evidence: *Bristol-Meyers Squibb Co. v. Apotex Inc.*, 2007 FCA 379, [2007] F.C.J. No. 1597 at para. 27. This is because the promise should be properly defined, within the context of the patent as a whole, through the eyes of the POSITA, in relation to the science and information available at the time of filing.

[142] Recently, Justice Hughes helpfully reviewed the concept of "the promise of the patent" in *Pfizer Canada Inc. v Mylan Pharmaceuticals ULC*, 2011 FC 547, 93 CPR (4th) 81, at paras 212-217. More specifically, Justice Hughes emphasized that "[i]n construing the specification of a patent, in particular the "promise", the Court is to look at the specification through the eyes of a person skilled in the art, bearing in mind commercial realities, being neither benevolent nor harsh, in order to determine fairly the true intent".

[143] It is also worth recalling the role of the promise of the patent with respect to utility. On behalf of the Federal Court of Appeal, Justice Laydon-Stevenson in *Ely Lilly Canada Inc.*, above, (FCA *Olanzapine*), at para 76, stated the following:

> [76] Where the specification does not promise a specific result, no particular level of utility is required; a "mere scintilla" of utility will suffice. However, where the specification sets out an explicit "promise", utility will be measured against that promise: *Consolboard*; *Pfizer Canada Inc. v. Canada (Minister of Health)* , [2009] 1 F.C.R. 253, 2008 FCA 108 (*Ranbaxy*). The question is whether the invention does what the patent promises it will do.
>
> [Emphasis added]

[144] At this juncture, the Court recalls that, on the one hand, Apotex submits that the promise of the '777 Patent relates to humans and, on the other hand, Sanofi submits that it merely relates to 'potential use' in humans.

[145] For the reasons that follow, the Court finds that the '777 Patent makes an explicit promise for use of the compound in humans.

[146] The Court will first summarize the expert evidence with regard to the promise of the patent.

(2) Summary of Expert Evidence

Dr. Hirsh

[147] Dr. Hirsh, on behalf of Apotex, opined that the ‘777 Patent is directed to the use of the dextro-rotatory enantiomer for use as a medicine for oral, rectal or parenteral administration for the purpose of treating and preventing platelet disorders due to extracorporeal blood circuits or the consequences of complications in atheroma. He also noted that the ‘777 Patent states that the dextro-rotatory enantiomer interferes with the mechanisms of arterial and venous thrombosis.

[148] Dr. Hirsh further explained to the Court that the description of the compound in the ‘777 Patent as being medicines and “active medicinal[s]” for therapeutic purposes would lead the haematologist/clinician to understand that this is a medicine for humans (rather than the laboratory rats used for the various tests reported in the ‘777 Patent). He also indicated that the diseases and conditions for which these compounds are promised to be useful in treating and preventing are clearly human diseases and conditions and that the dose administration section in the ‘777 Patent directs that the compound is for use in patients.

Dr. Byrn

[149] Dr. Byrn disagreed with Apotex’ experts including Dr. Hirsh’s interpretation of the promise of the ‘777 Patent. He stressed that pages 12 and 20 of the ‘777 Patent state that the results of these studies “demonstrate” that the “levo-rotatory isomer exhibits almost no platelet aggregation inhibiting activity and its toxicity is markedly higher than that of its dextro-rotatory homologue”. He

consequently concluded that the improvement in activity and toxicity (based on animal testing) means that the medicine of the invention (*i.e.* if and when the compound is used as medicine) can potentially be used for treatment. Dr. Byrn stated that a skilled pharmaceutical chemist would not understand the ‘777 Patent to be a promise of clinical approval, or a guarantee of use in humans.

[150] Dr. Byrn thus rejected the interpretation that the ‘777 Patent made a promise of a specific result. He also rejected that there was such a promise of use in humans. He further explained that advantages of the dextro-rotatory enantiomer having all of the activity and being better tolerated are set out in the patent and are clearly based on the animal test data included. It was his opinion that any pharmaceutical chemist would interpret the ‘777 Patent as telling the world that very interesting results had been obtained and thus one might expect similar results would be achieved in humans, but no clear promise or guarantee that such results would be achieved in humans.

Dr. Rodricks

[151] In Dr. Rodricks’ opinion, a person skilled in the art would understand from general biological principles that the combination of platelet aggregation inhibiting activity and reduced toxicity documented in the ‘777 Patent for the dextro-rotatory enantiomer would suggest that the dextro-rotatory enantiomer holds promise as a useful human drug. Such a person would know, however, that the ‘777 Patent does not guarantee that the enantiomer would be a successful human drug. He or she would know that such a determination would require much more intensive investigation of the efficacy and safety of the material of the type required by Health Canada or the US Food and Drug Administration than could be expected in a patent. The available

pharmacological and toxicological data would indicate to a person skilled in the art that the dextro-rotatory enantiomer was a worthy candidate for further investigation and development as a drug.

Dr. Shebuski

[152] In Dr. Shebuski's opinion, a person skilled in the art reading the '777 Patent would understand that it teaches that clopidogrel has platelet inhibiting activity and that this activity is not present in the other enantiomer. He further opined that the '777 Patent teaches that clopidogrel is better tolerated and less toxic than the other enantiomer and racemate. According to Dr. Shebuski, any person skilled in the art reading the '777 Patent would understand that these statements were based on animal testing. Given the knowledge at the time, he was of the view that a person skilled in the art would understand that these results indicate that clopidogrel's platelet inhibiting activity could lead to an antithrombotic effect and that, since a person skilled in the art would understand that a compound with platelet inhibiting activity could be a potential antithrombotic agent, it would be understood that clopidogrel had potential to be used as an antithrombotic medicine. Furthermore, given that the basis for the statements in the '777 Patent are the pharmacology studies conducted in rats, Dr. Shebuski opined that a person skilled in the art would not understand the teachings of the '777 Patent to be promising a specific result in humans. He therefore disagreed with Apotex' experts that the '777 Patent is explicitly promising that clopidogrel will be useful in humans in "the treatment and prevention of platelet disorders due to extracorporeal blood circuits or the consequence of complications in atheroma".

[153] In Dr. Shebuski's opinion, Apotex' experts' focus on the human use of clopidogrel is inconsistent with how a person skilled in the art would understand the claims and the teachings of

the ‘777 Patent. He opined that a person skilled in the art would read the ‘777 Patent and note the following: (1) the first page of the ‘777 Patent focuses on the structure of clopidogrel and its advantages; (2) almost half of the disclosure (pages 2-11) relates to chemistry (*i.e*. process information and examples); (3) the pharmacological testing was conducted in rats; and (4) based on the information before it, page 21 sets out potential uses for clopidogrel.

[154] Thus, Dr. Shebuski discarded Apotex’ experts’ reliance upon page 21 of the ‘777 Patent and their opinion that the ‘777 Patent made a promise that clopidogrel will have utility as a medicine in humans for the treatment and prevention of platelet disorders due to extracorporeal blood circuits or the consequence of complications in atheroma.

[155] Additionally, Dr. Shebuski opined that the opening line at page 21 is “On account of its interesting inhibitory properties towards platelet aggregation and its interference in the mechanism of formation of arterial and venous thromboses….”. He stated that the basis for this statement is the interesting properties identified in the pharmacological study conducted in rats and that a person skilled in the art would understand that this one (1) paragraph contains an explanation of how clopidogrel could be put to therapeutic use. In particular, he opined that the inventors were stating that, in light of the interesting pharmacological properties observed in the rat studies, clopidogrel has the potential to be used in the treatment and prevention of platelet disorders due to extracorporeal blood circuits or the consequences of complications in atheroma.

[156] Based on his reading of the ‘777 Patent and in particular the testing that is reported in the ‘777 Patent, Dr. Shebuski concluded that if there were a promise of a specific result, it is that

clopidogrel has a platelet aggregation inhibiting activity and is better tolerated than the levo-rotatory enantiomer. According to Dr. Shebuski, a person skilled in the art would not have read the ‘777 Patent as promising a specific result of clinical use in the treatment and prevention of platelet disorders due to extracorporeal blood circuits or the consequences of complications in atheroma.

[157] Having summarized the expert evidence, the Court will now turn to consider the following question: What is the promise of the ‘777 Patent?

(3) What is the Promise of the ‘777 Patent?

[158] In this case, the question of the promise of the patent is whether the ‘777 Patent promises a result in humans, as argued by Apotex, or whether it merely promises potential use in humans, as argued by Sanofi. From the outset, the Court observes that neither the word “humans” nor the words “potential use in humans” are to be found in the ‘777 Patent.

[159] In addressing the question of the promise of the patent, the Court will construe the promise in a purposive manner in accordance with the approach summarized by the Federal Court of Appeal in *Olanzapine*.

[160] At this stage, it is also important to reiterate that determining the promise of a patent is a question of law (*Bristol-Myers Squibb Co. v Apotex Inc.*, 2007 FCA 379, [2007] FCJ No 1597, at para 27).

[161] With the guiding principles of the FCA *Olanzapine* decision in mind and in order to determine the promise of the patent, the Court will now consider: (1) the wording in the ‘777 Patent; and (2) the relationship to the ‘875 genus Patent.

(1) *The Wording in the ‘777 Patent*

[162] When read as a whole and with a purposive approach, the wording used in the ‘777 Patent provides a number of indications that it promises in humans. In this regard, the Court finds the expert testimony of Dr. Hirsh, as summarized earlier, to be more persuasive than the expert tertimony of Dr. Byrn, Dr. Rodricks and Dr. Shebuski.

[163] Indeed, the Court finds the wording used throughout the ‘777 Patent as making an explicit promise in humans, as argued by Apotex, as opposed to a mere indication of a potential purpose that the “medicine of the invention” could be put to use, as argued by Sanofi. The following wording in the ‘777 Patent is particularly revealing:

- “**medicine**” – The compounds are described as medicines and active medicinals for therapeutic purposes. The Patent indicates that clopidogrel has a better therapeutic index than the salt of the racemic mixture (p. 12). The Patent explains that clopidogrel is to be used for patients by oral, rectal or parenteral administration. Based on this wording, it would be reasonable for the POSITA to understand that clopidogrel is a medicine for humans rather than for rats.

- “**patient**” – The dose administration in the patent directs that the compound is for use in patients.

- “**pharmaceutical compositions**” – The ‘777 Patent informs that the compound is an oil but that the salts play an important role as they allow the transformation of the oil tablets. The ‘777 Patent further states that clopidogrel, as an oily product, is more difficult to purify and is difficult to use for the preparation of pharmaceutical compositions. In addition, it mentions a daily

dose range for the tablets varying from 0.0001 to 0.500 grams. Significantly, the '777 Patent indicates that the dosage will depend on the age of the patient and the severity of the disorder to be treated.

- "**Active pharmaceutical index**" – is referred to in the '777 Patent which is intended for pharmaceutical use. Typically, active ingredients can be said to be given in the powder form but instead they are formulated into dosage forms *i.e.* tablets, capsules, and other dosage forms that are useful for administration.

- "**medicine of invention**" – As the Court concluded earlier, "medicine of the invention", as referred to in the '777 Patent, relates to clopidogrel.

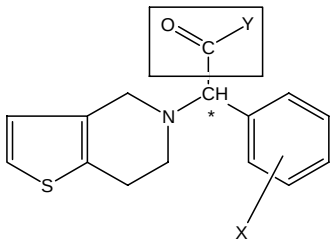
- "**Page 21 of the Patent**" – As the Court also concluded earlier, the Court's finding in section H related to page 21 of the '777 Patent that "the medicine of the invention can be usefully administered in the treatment and prevention of platelet disorders due to extracorporeal blood circuits or the consequence of complications in atheroma" confirms that clopidogrel on account of its properties can be used in the treatment of certain thrombotic human diseases.

[164] All of the above illustrate that the '777 Patent promises in humans. However, in this case, a look at the context leading to the selection '777 Patent is also informative in reaching this conclusion. Thus, the Court turns to the relationship between the '875 genus Patent and the '777 selection Patent.

(2) *The Relationship between the '875 Genus Patent and the '777 Selection Patent*

[165] In order to assess the promise of the '777 selection Patent, it is helpful to consider the '875 genus Patent from which the compound in the '777 Patent was selected.

[166] Canadian Patent No. 1,194,875 (the ‘875 Patent) was filed in Canada on July 8, 1983 and issued on October 8, 1985. This patent relates to a large genus consisting of approximately 9.5 million different compounds. The compounds disclosed in the ‘875 Patent are racemates. The general formula in the ‘875 Patent is as follows:



[167] Clopidogrel bisulfate is encompassed within the scope of the claims of the ‘875 Patent and was selected from this class of compounds.

[168] The ‘875 Patent specifically mentions the applications of the compounds in human and veterinary therapeutics. Of significance is the following paragraph at page 12 of the ‘875 Patent:

> The toxicological and pharmaceutical investigations reported above demonstrate the low toxicity of the compounds of the invention, as well as their excellent tolerance and their inhibiting properties on blood-platelet aggregation, and their antithrombotic activity, which make them very useful in <u>human</u> and veterinary therapeutic applications.
>
> [Emphasis added]

[169] Since the ‘875 Patent is the genus patent to the ‘777 Patent and that the ‘875 Patent explicitly refers to humans, the Court cannot accept Sanofi’s contention that the promise of the ‘777 Patent is a mere potential in humans. Accepting Sanofi’s contention would mean accepting that the selection ‘777 Patent promises less than the ‘875 genus Patent. In this regard, the Court recalls the

conditions for a valid selection patent as defined in *I.G. Farbenindustrie A.G.'s Patents, Re* (1930), 47 R.P.C. 289 (Eng. Ch. Div.), at pp 322-23:

> 1. There must be a substantial advantage to be secured or disadvantage to be avoided by the use of the selected members.
>
> 2. The whole of the selected members (subject to "a few exceptions here and there") possess the advantage in question.
>
> 3. The selection must be in respect of a quality of a special character peculiar to the selected group. If further research revealed a small number of unselected compounds possessing the same advantage, that would not invalidate the selection patent. However, if research showed that a larger number of unselected compounds possessed the same advantage, the quality of the compound claimed in the selection patent would not be of a special character.

[170] Reading these conditions as a whole, it would be illogical to allow a selection patent to promise less than the genus patent – as the basic requirement for a selection patent is that it offers to the public a special advantage or character not disclosed by the genus. Although the Court would not go so far as to rule out that in some circumstances a selection patent could promise less than its genus patent, in the case at bar, the evidence leads the Court to find that this cannot be so.

[171] In addition, although not determinative for the construction of a promise of a patent, the history of the development of the '777 Patent leads one to believe that the discovery of the invention of the '777 Patent was intended for human use. The selection '777 Patent does not promise less than its genus '875 Patent for the following reasons:

- the previous use of ticlopidine was in humans;
- the fact that ticlopidine is part of thienopyridine compounds;
- the work conducted by Sanofi to find a more potent drug than ticlopidine with a better risk/benefit ratio leading to the '875 genus Patent;

- the ‘875 genus Patent, like ticlopidine, is also part of the thienopyride compounds; and
- the ‘875 genus Patent explicitly refers to humans.

(3) *The Court’s Conclusion on the Promise of the Patent*

[172] As noted earlier, the Court is cognizant of the fact that the word “humans” is not explicitly found in the ‘777 Patent. However, a purposive interpretation of the ‘777 Patent has led the Court to find that the ‘777 selection Patent cannot promise less than the ‘875 genus Patent and this finding is, as explained earlier, supported by the wording in the ‘777 Patent.

[173] In the circumstances, the Court accordingly concludes that the POSITA would understand that the promise in the ‘777 Patent is in humans. It follows that the Court cannot accept Sanofi’s position regarding the promise of the patent because to do so would totally ignore the work conducted prior to the ‘777 selection Patent and would amount to a reading down of the promise. This would also be inconsistent with the understanding of a person skilled in the art with respect to the well-known ticlopidine drug, the ‘875 Patent and the wording of the ‘777 Patent, including medicine, medicinal, patient, dosage, tablets, capsules, and pharmaceutical compositions.

[174] In summary, the Court concludes that the POSITA would find the promise respecting the use of the invention of the ‘777 Patent to be a use in humans.

[175] Notwithstanding the above, the Court must now consider a final argument advanced by Sanofi, referred to as the “matching principle” argument.

(4) *Sanofi’s “Matching Principle” Argument*

[176] During final arguments, Sanofi raises before the Court the concept of the "matching principle" in connection with the promise of the patent.

[177] More particularly, counsel for Sanofi refers to the Federal Court of Appeal's recent decision in *Eli Lilly* (*Olanzapine)*, above, which dealt with the '113 Patent, a selection patent for the compound olanzapine. In that case, Sanofi alleges that the Federal Court of Appeal reminded litigants and the lower courts that the construction of the utility of a patent must be consistent with the information in a patent and how a POSITA could interpret that information. Sanofi further submits that, in *Eli Lilly* (*Olanzapine)*, the Federal Court of Appeal criticized Teva for taking the position that a particular animal model was not predictive of what would occur in humans, but at the same time also taking the position that a POSITA would read the patent as promising an effect in humans. In support of its argument, Sanofi refers to paras 102 and 103 in *Eli Lilly* (*Olanzapine)*:

> [102] To illustrate, I refer to an example. In addressing the alleged advantages (to which I will return later), the trial judge noted that "Novopharm contested on numerous grounds the assertion in the '113 Patent about olanzapine's advantage with respect to cholesterol" (para. 80). Among other things, Novopharm disputed the viability of using a dog model for predicting cholesterol effect in humans. The trial judge briefly reviewed the evidence of three experts in this respect. Only one, Dr. Bauer, felt the dog was a good model for predicting cholesterol effects in humans. However, his theory had been developed after the '113 Patent was filed. He agreed that the prevailing view in 1991 was that the dog was not a good model for cholesterol studies.
>
> [103] Therefore, the unanimous opinion (on the basis of the evidence referred to) was that the dog was not a good model for cholesterol studies. Notwithstanding, the trial judge concludes that "the reference in the '113 Patent to the dog study and the cholesterol findings implies a concern about the potential effect in humans" (paras. 37, 38, 52, 93). Query, when the unanimous expert opinion was that the dog was not a good model for predicting cholesterol effects in humans, how could it be that a POSITA would read the reference to cholesterol levels in dogs as implying a concern about its potential effect in humans?
>
> [Emphasis added]

[178] The Court understands the "matching principle" argument advanced by Sanofi that states that the construction of the promise of a patent must be consistent with the information in a patent and how a POSITA would interpret that information. In this case, according to Sanofi, this would mean that there are no promises beyond the rats (rodents) because the data in the '777 Patent relates solely to rats. In support of its argument, Sanofi submits the following options for interpreting the promise of the '777 Patent:

- Option 1: If POSITA would understand rat studies in patent to be predictive of activity in humans, then patent promises potential activity in humans.
- Option 2: If POSITA would understand rat studies in patent not to be predictive of activity in humans, then patent does not promise any activity in humans.
- Option 3 (Sanofi asserted that this was Apotex' position): POSITA would understand rat studies in patent not to be predictive of activity in humans, but finds patent promises activity in humans.

[179] In the Court's opinion, the problem with Sanofi's concept of the "matching principle" and its possible options would require the Court to look at the information in the '777 Patent from the prism of the rat studies data and, from that data, provide a construction of the patent that must be consistent with that information and how a POSITA would interpret that information.

[180] However, the Court does not interpret the decision in *Eli Lilly* (*Olanzapine)*, above, in the manner urged by Sanofi. Sanofi would like the Court to look at the rat studies data and construe the promise on the basis of that data. But this would lead to the illogical result that the promise of a particular patent could never be in humans if there is no human data in the patent itself. The Court's understanding of the guidance stemming from the Federal Court of Appeal in *Eli Lilly* (*Olanzapine)* above, as enunciated by Justice Layden-Stevenson, is that a reading of the entire patent is necessary

to determine whether there is a promise and, only then, to consider whether the data supports the promise. The Court does not understand the teaching of the Federal Court of Appeal as reading first the data and assessing the promise of the ‘777 Patent in light of that data.

[181] In light of the above, the Court cannot accept Sanofi’s “matching principle” argument in the circumstances.

K. *Summary on Claims Construction*

[182] After considering the words of the claims at issue of the ‘777 Patent and also considering the expert evidence, the Court concludes that the relevant claims of the patent should be construed as follows:

- Claim 1 relates to substantially pure clopidogrel and its pharmaceutically acceptable salts.
- Claim 3 relates to substantially pure clopidogrel bisulfate.
- Claim 6 relates to the process for the preparation of the clopidogrel and its pharmaceutically acceptable salts including the use of “optically active acid” acid and solvents that result in the preparation of substantially pure clopidogrel and its pharmaceutically acceptable salts following the process described in claim 6.
- Claim 10 relates to the pharmaceutical composition of substantially pure clopidogrel and its pharmaceutically acceptable salts in an effective amount as active ingredient.
- Claim 11 relates to the pharmaceutical composition of substantially pure clopidogrel and its pharmaceutically acceptable salts in an effective amount as active ingredient.

[183] Having established the proper construction of the relevant claims of the ‘777 Patent, the Court now turns to the question of infringement.

VI Infringement – Background

A. *Introduction*

[184] This proceeding consolidates two actions. The first (T-644-09) was the action by Apotex to impeach the ‘777 Patent and to declare Apotex’ proposed sale of clopidogrel tablets in Canada to be non-infringing of the claims of the ‘777 Patent. The second (T-933-09), which will now be determined by the Court, is Sanofi’s action for infringement of the ‘777 Patent. Sanofi argues that if the ‘777 Patent is valid, there is no debate that Apotex infringed product Claims 1, 3, 10 and 11 of the patent and the process claims – more particularly Claims 6 and 7. In response, Apotex asserts that its processes of manufacture do not infringe the product and the process claims of the ‘777 Patent. Given the Court’s findings that the ‘777 Patent is invalid, which will be discussed in more detail later in the decision, the issue of infringement is in principle moot. Nonetheless, the Court will address the issue in order to respond to the views advanced by the parties in this regard, in the event this could potentially be of assistance.

B. *General Principles*

[185] Although the *Patent Act* does not provide a definition of “infringement”, s 44 of the Act (now s 42) outlines the exclusive rights granted to a patentee:

GRANT OF PATENTS	CONCESSION DES BREVETS
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44. Every patent granted under this Act shall contain the title or name of the invention, with a reference to the specification, and shall, subject to the conditions prescribed in this Act, grant to the patentee and his legal representatives for the term therein mentioned, from the granting of the patent, the exclusive right, privilege and liberty of making, constructing, using and vending to others to be used the invention, subject to adjudication in respect thereof before any court of competent jurisdiction.

44. Tout brevet accordé en vertu de la présente loi contient le titre ou nom de l'invention, avec renvoi au mémoire descriptif, et accorde, sous réserve des conditions prescrites dans la présente loi, au breveté et à ses représentants légaux, pour la durée du brevet y mentionnée, à partir de la date de la concession du brevet, le droit, la faculté et le privilège exclusifs de fabriquer, construire, exploiter et vendre à d'autres, pour qu'ils l'exploitent, l'objet de l'invention, sauf jugement en l'espèce par un tribunal compétent.

GRANT OF PATENTS

OCTROI DES BREVETS

Contents of patent

Contenu du brevet

42. Every patent granted under this Act shall contain the title or name of the invention, with a reference to the specification, and shall, subject to this Act, grant to the patentee and the patentee's legal representatives for the term of the patent, from the granting of the patent, the exclusive right, privilege and liberty of making, constructing and using the invention and selling it to others to be used, subject to adjudication in respect thereof before any court of competent jurisdiction.

42. Tout brevet accordé en vertu de la présente loi contient le titre ou le nom de l'invention avec renvoi au mémoire descriptif et accorde, sous réserve des autres dispositions de la présente loi, au breveté et à ses représentants légaux, pour la durée du brevet à compter de la date où il a été accordé, le droit, la faculté et le privilège exclusif de fabriquer, construire, exploiter et vendre à d'autres, pour qu'ils l'exploitent, l'objet de l'invention, sauf jugement en l'espèce par un tribunal compétent.

[186] In *Monsanto Canada Inc. v Schmeiser*, 2004 SCC 34, 31 CPR (4th) 161, at para 35, the Supreme Court of Canada held that in order to determine if there was infringement, the question to be asked is the following: Did the defendant's activity deprive the inventor, in whole or in part, directly or indirectly, of full enjoyment of the monopoly conferred by law? That monopoly is the exclusive right, privilege and liberty of making, constructing, using, vending and importing the invention to others to be used, subject to adjudication.

[187] It is not disputed that the burden of proving infringement rests on the plaintiffs based on the balance of probabilities (see *Eli Lilly and Co. v Apotex Inc.*, 2009 FC 991, 80 CPR (4th) 1, [*Cefaclor*], at para 211; *Weatherford Canada Ltd. v Corlac Inc.*, 2010 FC 602, 84 CPR (4th) 237, at para 170; *Lubrizol Corp. v Imperial Oil Ltd.* (FCA), [1992] FCJ No 1110, 45 CPR (3rd) 449).

[188] Furthermore, the question of infringement is a mixed question of fact and law, as explained in Hughes and Woodley, *Patents*, 2nd ed (Markham, ON: LexisNexis, 2005) at 375:

> […] The question of infringement is a mixed question of fact and law. The construction and scope of the patent is a matter of law; whether the defendant's activities fall within the scope of the patent is a question of fact, the burden being on the patentee to prove infringement. […]

[189] The guiding principles regarding the concept of "use" under s 42 of the *Patent Act* were outlined in a comprehensive manner in *Monsanto*, above, at para 58, as follows:

> [58] …
> 1. "Use" or "*exploiter*", in their ordinary dictionary meaning, denote utilization with a view to production or advantage.

> 2. The basic principle in determining whether the defendant has "used" a patented invention [page 927] is whether the inventor has been deprived, in whole or in part, directly or indirectly, of the full enjoyment of the monopoly conferred by the patent.
>
> 3. If there is a commercial benefit to be derived from the invention, it belongs to the patent holder.
>
> 4. It is no bar to a finding of infringement that the patented object or process is a part of or composes a broader unpatented structure or process, provided the patented invention is significant or important to the defendant's activities that involve the unpatented structure.
>
> 5. Possession of a patented object or an object incorporating a patented feature may constitute "use" of the object's stand-by or insurance utility and thus constitute infringement.
>
> 6. Possession, at least in commercial circumstances, raises a rebuttable presumption of "use".
>
> 7. While intention is generally irrelevant to determining whether there has been "use" and hence infringement, the absence of intention to employ or gain any advantage from the invention may be relevant to rebutting the presumption of use raised by possession.

[190] It is further recalled that intention is not material to a finding of infringement. However, intention plays an important role in determining the nature of the remedy. Punitive damages may be affected by whether or not there was knowledge or intent (*Monsanto*, above, at para 86).

[191] Justice Gauthier of the Federal Court, as she then was, in *Cefaclor* provided a full and comprehensive analysis on this issue of importation and infringement. At para 318, Justice Gauthier reiterated that the monopoly granted to a patentee extends so as to preclude the importation into Canada of products made abroad in accordance with processes that would, if practiced in Canada, constitute an infringement of the patent:

> [318] … Importation of products made abroad that are the subject of patented process claims in Canada is prohibited. This prohibition is widely recognized and is well-settled law in Canada.

[192] It has also been held that the export from Canada of a patented product to be used abroad is considered to be an act of infringement (*AlliedSignal Inc. v Du Pont Canada Inc. et al.* (1995), 61 CPR (3d) 417 (FCA).

[193] When addressing a question of infringement, the Court must first construe the claims. Once the construction and scope of the claims have been determined, the Court must then determine if the patentee has successfully proven that said claims have been infringed.

C. *Summary of Sanofi's Case on Infringement*

[194] Sanofi argues that Apotex' activities constitute acts of infringement. According to Sanofi, Apotex infringed the '777 Patent because Apotex imported, offered for sale, sold, made, possessed for commercial purposes, used and exported clopidogrel bisulfate and clopidogrel bisulfate tablets. Sanofi asserts that these acts constitute use of the invention of the '777 Patent which deprives Sanofi, the patentee, and BMS, its exclusive licensee, of the full enjoyment of the monopoly granted and the right to exclude others from practicing the invention of the '777 Patent. More particularly, the alleged infringement results from the following activities:

- [omitted];
- [omitted];
- [omitted]; and
- [omitted].

[195] In response, Apotex has argued that the process employed by its supplier located in […] […] falls outside of Claim 6. Sanofi, on the other hand, maintains that it is clear that the process used is within Claim 6 and that Apotex is importing the product of this process. Sanofi further asserts that the alleged differences are minor variations from the process literally described in the disclosure of the patent and that the process thus still falls within the wording of Claim 6. Sanofi also argues that the defences advanced by Apotex, *i.e.* the limitation period defence and the defence based on the Settlement Agreements, estoppel and abuse of process, are unfounded in both fact and law.

[196] Consequently, Sanofi submits it is entitled to all damages arising from Apotex' infringing acts or disgorgement of the profits unjustly gained by Apotex, as Sanofi may elect. In addition, Sanofi seeks an injunction and the delivery up of all bulk clopidogrel and tableted clopidogrel within the possession, power or control of Apotex and Pharmachem.

[197] Given the Court's finding with respect to utility and obviousness, there is no need at this stage to decide on a possible injunction or the award of damages and interest. Therefore, the Court's analysis will focus essentially on infringement, and in light of the foregoing, the Court will now determine if the patentee, Sanofi, has met its burden of demonstrating that Apotex infringed the claims of the '777 Patent.

D. *The Evidence before the Court*

[198] The Court recalls that during trial, Dr. Bernard Sherman, the Chair of Apotex, testified that the decision had been made to develop a clopidogrel bisulfate product because it was going to be commercially successful. [omitted] .

[199] [omitted] .

[200] [omitted] .

[201] [omitted] .

[202] According to the evidence, Apotex began acquiring significant quantities of clopidogrel bisulfate from […] in early 2004 and continues to receive material to this day. Apotex has received over 80,000 kilograms of clopidogrel, which represents a value to Apotex of about 1.6 billion USD on the U.S. market at Apotex' selling price.

[203] It was also submitted in evidence that the bulk clopidogrel received by Apotex from […] was delivered by an agent of […] to Air Canada and delivered to Canada pursuant to an Air Waybill issued out of Montreal. Notwithstanding the fact that from February 13, 2006, the shipments were indicated to be on a CIF basis and that prior to that date they are indicated to be on a DDU (delivered duty unpaid) basis, it can be seen on the Air Waybills and the Canada Customs Coding Forms that Apotex is the "importer" for the purposes of Canada customs declarations. Thus, the Court finds, as argued by Sanofi, that Apotex' importation of clopidogrel bisulfate constitutes an act of infringement (see *Schmeiser*, above, at para 44; *Cefaclor*, above, at paras 270-329).

[204] Once the goods clear customs, the bulk clopidogrel imported by Apotex is then trucked to Apotex' manufacturing plant where it is formulated into tablets containing 75 mg of clopidogrel bisulfate and henceforth ready for sale.

[205] In addition to having sold large quantities of clopidogrel bisulfate 75 mg tablets in a variety of countries, Apotex sold approximately 500 million tablets to the U.S. market between August 8, 2006 and August 31, 2006 until it was enjoined to cease these sales by the U.S. District Court Southern District of New York on October 23, 2009, in view of the U.S. Patent. During trial, Sanofi brought to the attention of the Court that after this injunction was issued, it is not clear what became of the unsold material, *i.e.* whether it was returned to Canada, shipped to other countries or retained in the U.S. During cross-examination, [omitted]:

Q. [omitted]?
A. [omitted].
Q. [omitted]?
A. [omitted].
Q. [omitted]?
A. [omitted].
Q. [omitted]?
A. [omitted].
Q. [omitted]?
A. [omitted].
Q. [omitted]?
A. [omitted].

[206] At an average selling price of $2.00 per tablet, the value to Apotex of the sale of the missing tablets would represent approximately 1 billion USD. The lack of evidence regarding these missing tablets is certainly perplexing.

[207] The evidence further demonstrates that Apotex sold clopidogrel bisulfate to numerous other countries. As of January 15, 2011, Apotex had received and filled purchase orders in Canada for over 77 million tablets transported to Hong Kong, New Zealand, Iran, Libya, Malaysia, Singapore, Oman, Haiti, Moldova, Thailand, Hungary, the Philippines, Ukraine, Sierra, Australia, etc. Sanofi submits that the acceptance of purchase orders and manufacture in Canada and sale for export are further infringing acts committed by Apotex (see *AlliedSignal Inc.*, above, at paras 72-73). The Court, based on the evidence, agrees and so finds.

[208] Sanofi also submits that the possession of a patented good for a commercial purpose is an act of infringement (see *Schmeiser*, above, at paras 46-58). In support of this claim, Sanofi explained to the Court that with respect to the U.S. sales by Apotex to Apotex Corp., the purchase orders were received and processed in Canada. Although the commercial invoices for the U.S. sales do not indicate any commercial terms, Apotex appropriates the goods in fulfillment of these purchase orders and accordingly the transfer of title occurs in Canada. Hence, the Court again agrees with Sanofi that, based on the evidence, Apotex committed an act of infringement by possessing the patented good at issue for commercial purposes.

[209] In the customs documentation, Apotex is represented by Apotex' U.S. customs agent, Affiliated Customs Brokers of Detroit, Michigan, as the importer of record. After the goods are cleared through U.S. customs by the agent of Apotex, they are shipped to the warehouse of Apotex Corp., Apotex' U.S. marketing entity. The sales by Apotex Corp. are made pursuant to an Abbreviated New Drug Application (ANDA) in the name of Apotex and regulatory approval obtained by Apotex Inc. with Apotex Corp. acting as its agent.

[210] Based on all of these findings of infringing acts, it is clear that Apotex acted in a manner that interferes with the full enjoyment of the monopoly that had been granted to Sanofi. The Court concludes that Apotex committed acts of infringement by manufacturing, using, importing, exporting, possessing and selling a product protected by the '777 Patent without the permission of Sanofi. The Court will now examine how the infringing acts relate to the product claims and the process claims.

(1) Product Claims: Claims 1, 3, 10 and 11

[211] The Court recalls Apotex' pleadings with respect to the issue of the enantiomeric purity of the clopidogrel referred to in Claims 1, 3 10 and 11. As concluded earlier, experts on both sides have agreed that the purity of the clopidogrel claimed in the '777 Patent is substantial purity. Hence, there is no issue with respect to the construction of Claims 1 and 3 of the '777 Patent, which relates to substantially pure clopidogrel bisulfate.

[212] With respect to Claims 10 and 11, there is no dispute that they relate to pharmaceutical compositions containing clopidogrel or its pharmaceutically acceptable salts.

[213] In light of the evidence that was before the Court, there is no question that the acts committed by Apotex infringe Claims 1, 3, 10 and 11 of the '777 Patent. The Court agrees with Sanofi that the product claims were infringed by virtue of Apotex having made, used, possessed and sold clopidogrel bisulfate and pharmaceutical compositions (75mg tablets) containing clopidogrel bisulfate for others to be used.

(2) Process Claims: Claims 6 to 9

[214] First and foremost, Sanofi claims that Apotex' supplier, […], used a process to produce bulk clopidogrel which infringes Claim 6 of the '777 Patent, and that Apotex furthermore imported the product of that process.

[215] In this regard, Sanofi relies on subsection 39(2) of the *Patent Act* and contends that where a patent claims a process to make a new product, "any substance of the same chemical composition and constitution shall, in the absence of proof to the contrary, be deemed to have been produced by the patented process" (subsection 39(2) of the *Patent Act*).

[216] Subsection 39(2) of the Act therefore imposes the burden of proof on Apotex to demonstrate that its supplier's process does not infringe any of the process claims. The Court observes that Sanofi's infringement argument on process claims principally concerns Claims 6 and 7.

[217] In *Free World Trust v Électro Santé Inc*., 2000 SCC 66, 9 CPR (4th) 168, at paras 55-57, the Supreme Court of Canada held the following with regards to process infringement:

> [55] It would be unfair to allow a patent monopoly to be breached with impunity by a copycat device that simply switched bells and whistles, to escape the literal claims of the patent. Thus the elements of the invention are identified as either essential elements (where substitution of another element or omission takes the device outside the monopoly), or non-essential elements (where substitution or omission is not necessarily fatal to an allegation of infringement). For an element to be considered non-essential and thus substitutable, it must be shown either (i) that on a purposive construction of the words of the claim it was clearly not intended to be essential, or (ii) that at the date of publication of the patent, the skilled addressees would have appreciated that a particular

element could be substituted without affecting the working of the invention, i.e., had the skilled worker at that time been told of both the element specified in the claim and the variant and "asked whether the variant would obviously work in the same way", the answer would be yes: Improver Corp. v. Remington, supra, at p. 192. In this context, I think "work in the same way" should be taken for our purposes as meaning that the variant (or component) would perform substantially the same function in substantially the same way to obtain substantially the same result. In Improver Corp. v. Remington, Hoffmann J. attempted to reduce the essence of the Catnic analysis to a series of concise questions, at p. 182:

> (i) Does the variant have a material effect upon the way the invention works? If yes, the variant is outside the claim. If no: --
>
> (ii) Would this (i.e.: that the variant had no material effect) have been obvious at the date of publication of the patent to a reader skilled in the art? If no, the variant is outside the claim. If yes: --
>
> (iii) Would the reader skilled in the art nevertheless have understood from the language of the claim that the patentee intended that strict compliance with the primary meaning was an essential requirement of the invention? If yes, the variant is outside the claim.

[56] The three questions are not exhaustive but they encapsulate the heart of Lord Diplock's analysis, and have been endorsed in subsequent English cases.

[57] In AT & T Technologies, supra, at p. 257, Reed J. derived a series of interpretive principles from Catnic, supra, O'Hara, supra, and other cases. Her third principle is as follows:

> (3) if a variant of an aspect of a claim has no material effect on the way the invention works there is a presumption that the patent is infringed and that the patentee intended that that variant falls within the scope of the claim... [Emphasis in original]
>
> [Emphasis added]

[218] In sum, if modifications are brought into a claimed process but the essential elements remain, there is still infringement.

[219] Apotex maintains that the bulk clopidogrel bisulfate used in its Apo-clopidogrel tablets is manufactured by the process outlined in […] U.S. and Canadian Drug Master File. Sanofi submits that the steps in this process that are relevant to the infringement of Claim 6 are described in [omitted].

[220] Turning to Claim 6, as previously explained in the section on the construction of claims, this claim identifies a three (3) step process for the preparation of clopidogrel.

[221] Apotex' position is that Claim 6 should be read as limited to acetone as the solvent and to (*R*)-camphorulfonic acid as the optically active acid. Sanofi argues that this is too narrow a construction.

[222] The two relevant expert witnesses who testified on this issue were Dr. Adger, for Apotex and Dr. Byrn, for Sanofi. Dr. Adger opined that neither of the processes he was provided with by Apotex have the essential elements of Claim 6. Dr. Adger appeared to suggest that because the [omitted], it does not fall within the scope of any of the process claims of the '777 Patent.

[223] On the other hand, Dr. Byrn in his Expert Report, at para 173, concluded as follows:

> Thus in my opinion, the process described in these documents not only uses the teachings of the '777 Patent, but is within

> claim 6. The process described is a simple variation of what is specifically set out in the examples. [omitted]. The process though is within the words of claim 6. The product of the process is within claims 1 and 3.

[224] In support of his opinion, Dr. Byrn submitted a table to help the Court visualize the slight variation between Claim 6 and the […]. It is clear to the Court that the only difference is that the [omitted] :

Claim 6 Process	[omitted]
Formation of a salt of the racemate with an optically active acid in a solvent,	[omitted]
	[omitted]
Repeated recrystallization of the salt, are carried out until a product of constant optical rotatory power is obtained,	[omitted]
Liberate clopidogrel from its optically active salt using a base	[omitted]
If desired, add pharmaceutically acceptable acid to make clopidogrel salt	[omitted]

[225] In order to visually depict the two processes, Dr. Byrn submitted the following drawings:

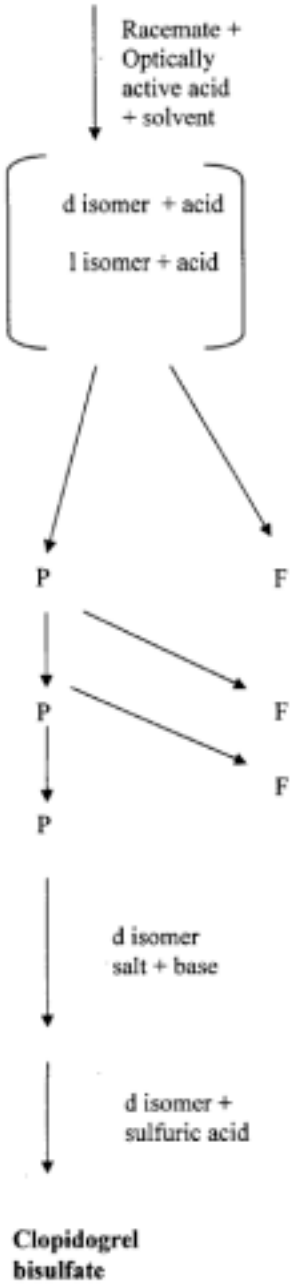
Claims 6 and 3 of the '777 Patent

(1) Formation of a salt of racemic methyl alpha-5 (4,5,6, 7-tetrahydro (3,2-c) thieno pyridyl (2-chlorophenyl) – acetate with an optically active acid in a solvent

(2) Repeated recrystallizations of the salt are carried out until a product of constant optical rotatory power is obtained

(3) Then the Dextro-rotatory isomer is liberated from its salt by a base

(4) Bisulfate salt of clopidogrel is formed with a pharmaceutically acceptable acid



Key:
P = Precipitate
F= Filtrate

Apotex' Documents

[omitted]

[226] In cross-examination, Dr. Adger, the expert for Apotex, agreed there was only a slight variation between Claim 6 and the […]. In fact, when asked to compare the two diagrams above, he characterized them as being "black and white" and agreed that they were almost mirror images of each other (Adger, cross T1781-1782):

Q. The process described taking the right hand side of the diagram on page 5 and switching it to the left?
A. It's like black and white.
Q. Or the reverse?
A. Right.
Q. It's like mirror images?
A. Almost.
Q. If you look at claim 6 and keep your tab 8, or the more detailed description that wasn't provided to you in front of you, you'd agree, following the resolution in tab 8, Clopidogrel is made?
A. Yes.
Q. [omitted]?
A. [omitted].
Q. [omitted]?
A. [omitted].
Q. [omitted]?
A. [omitted].

[227] Although Dr. Adger nuanced his answer in re-examination, Sanofi contends that Dr. Adger's only argument with respect to infringement is limited to the following aspect of Claim 6: the salt that is recrystallized to form the clopidogrel salt must be the same as the precipitate that forms initially from the addition of the optically acid salt to the racemic mixture.

[228] Dr. Byrn's testimony was useful in explaining that when the optically active salt is added to the racemic mixture, in both the Claim 6 process and the […], two optically active salts are formed, one of which stays in the solution (Byrn Report, para 171):

> [171] Dr. Adger's statement in paragraph 266 that "the salt did not arise from the racemic mixture but rather from an enantiomerically enriched sample" is simply pedagogical nonsense. The salt is the salt in solution and any synthetic or solid state chemist who understands salt formation would understand that claim 6 covers any separation regardless of whether the desired salt precipitates or remains in solution. The act of the precipitation enantiomerically enriches both the broth and the precipitated salt.

[229] In light of this evidence, the Court finds the testimony of Dr. Byrn to be more persuasive than the testimony of Dr. Adger. As clearly explained by Dr. Byrn, the only difference between the two processes is that an additional step is included in the [omitted]. This amounts to a mere tweaking of the process. Consequently, the Court considers that Apotex has infringed Claim 6 of the '777 Patent.

[230] As for Claim 7, which relates to the process described in Claim 6, it specifies levo-CSA as the optically active solid. [omitted]. Therefore, Apotex argues that the […] does not fall within the scope of Claim 7. As Sanofi pointed out, [omitted] and the Court accepts this argument.

[231] Finally, with regards to Claims 8 and 9, Apotex submits that the […] does not employ acetone. As already indicated in the discussion in connection with Claim 6, the Court does not accept that these claims should be read as limiting acetone as the solvent. Thus, in light of the evidence, the Court concludes that Apotex infringed the process Claims 6 to 9 of the '777 Patent.

E. *Potential Exemption from Liability*

[232] The common law has long recognized an exemption from liability for infringement known as the experimental use exemption. More particularly, an experimental user, without a licence, in the course of a *bona fide* experiment with a patented article is not, in law, an infringer. This exception, set out in s 55.2(1) of the *Patent Act* (post-October 1, 1989), provides that it is not an infringement to use the invention solely for uses reasonably related to the development and submission of information required by law:

Exception	Exception
55.2 (1) It is not an infringement of a patent for any person to make, construct, use or sell the patented invention solely for uses reasonably related to the development and submission of information required under any law of Canada, a province or a country other than Canada that regulates the manufacture, construction, use or sale of any product.	**55.2** (1) Il n'y a pas contrefaçon de brevet lorsque l'utilisation, la fabrication, la construction ou la vente d'une invention brevetée se justifie dans la seule mesure nécessaire à la préparation et à la production du dossier d'information qu'oblige à fournir une loi fédérale, provinciale ou étrangère réglementant la fabrication, la construction, l'utilisation ou la vente d'un produit.

(1) Apotex' Alleged Experimental Use

[233] Canadian courts have consistently held that the use of a patented invention for the purpose of submission to regulatory authorities was exempt from infringement (see *Smith Kline & French Inter-American Corp. v Micro Chemicals Ltd.*, [1972] SCR 506; *Merck & Co. Inc. v Apotex Inc.*, 2006 FC 524, [2006] FCJ No 671, at paras 157-161, rev'd on other grounds, 2006 FCA 323, [2006] FCJ No 1490). Apotex relies on this exception to argue that it should not be held liable for any infringement relating to its experimental and regulatory uses of clopidogrel.

[234] In support of its position, Apotex relies on the testimony of Mr. Fahner who reviewed the documents relating to Apotex' use of clopidogrel for regulatory purpose. Mr. Fahner prepared charts which identified the amount of raw material from each lot it received that Apotex used for the various research and development activities involved in the formulation development process, and charts which identified the amounts of clopidogrel from each lot Apotex received that were sampled and retained for ongoing regulatory purposes, or consumed in complying with the regulatory requirements for in-process quality controls.

[235] Notwithstanding the fact that Sanofi did not challenge the application of the exception, Sanofi did object in respect of certain specific lots on the basis that no documents were provided that would show that the material was used solely for regulatory purposes.

[236] In the present case, the evidence shows that there has been a use of clopidogrel that should be considered in the circumstance of "fair dealing". However, the Court is not convinced that Apotex met its burden of proving that such an exception applies. Apotex failed to provide the Court with evidence relating to what was ultimately done with the bulk material or tablets. Accordingly, [omitted] :

Q. [omitted]?
A. [omitted].
Q. [omitted]?
A. [omitted].
Q. [omitted]?
A. [omitted].

[237] Mr. Barber also testified about which records would be available within Apotex' SAP system (Apotex' inventory system) (Barber, cross T1064-1065). The evidence demonstrates that Apotex does not keep a record of inventory of tablets made for regulatory purposes:

> Q. And the SAP system we are looking at here, it's supposed to collect all information for inventory purposes; that's one of its purposes?
> A. I guess it depends what you mean by "all information", I am not sure.
> Q. Well, it would record receipt of bulk material?
> A. Yes, it would.
> Q. It would record transfer of bulk material to the formulation department?
> A. Yes, it would.
> Q. It would record how many tablets had been created from that material?
> A. It would if it's a commercial product. Formulation development tablets are not in the SAP system.
> Q. Okay.
> A. So the raw material aspect of what formulation development does is captured there, but anything we turn into trials is not in SAP.
> Q. Let''s deal with the commercial side.
> A. Okay.
> Q. It would also include sales of the tablets?
> A. I believe it would, yes.
> Q. And would it also include material that might have to be destroyed for any purpose; stale-dated product, let's say?
> A. It would reconcile it somehow. I don't know if it would show it was destroyed. There would be a record, a paper record of the destruction and some way of reconciling that amount in SAP.
> Q. Okay. And are you aware that Apotex on occasion, has transferred regulatory material into commercial material?
> A. No, I am not aware that's ever happened.
> Q. You are not aware of that ever occurring?
> A. I am not aware that's ever happened.
> Q. Okay. If that did happen, the SAP system would record that?
> A. I don't think we have any other way of selling it if it's not within the system, so I think it would have to be.
> Q. Do you keep inventory of bulk that's left on hand?
> A. Bulk of what?
> Q. Bulk clopidogrel bisulphate.
> A. Of formulation development trials, or...

Q. Does the SAP system, if you punched in whatever numbers, could you get the amount of bulk sitting in the warehouse today?
A. Of raw material, yes.
Q. Okay, could you also plug in and figure out how many tablets were sitting in the warehouse today?
A. Commercial tablets, yes.
Q. Yes. What about regulatory?
A. No.
Q. So you don't keep a record of inventory of, let's say, hundreds of thousands of tablets that was made for regulatory purposes?
A. No, the regulatory aspect doesn't require anything to happen in SAP. Again, formulation development makes our batches outside of SAP system. At the time when a product is being developed, SAP is not structured necessarily to receive all that information, and we go through so many iterations of formulations and that would all require a separate development of codes and stuff to manage that, and it's just not practical for us to do that.
Q. Are records kept as to what happens to regulatory material?
A. We would have records, yes.
Q. And those records would include how it was utilized, and you have included some of those here?
A. Yes. And executed batch records would be one of the records we'd have in terms of how much we produced.
Q. And would you have an inventory record of what happened to that material after it was utilized?
A. We don't have inventory records per se, but we do keep the inventory and, we would have it on file there and we could verify the amount that's present at any given point in time. Also if we destroy it, there would be a destruction record that shows how much we destroyed.
Q. Okay, so there should be destruction records if things were destroyed?
A. Yes.

[238] In light of the absence of records regarding inventory of regulatory material and given Apotex' failure to tender evidence as to the alleged destruction records of the disputed lots, the Court cannot rule out the possibility that all or some of the raw material or the actual formulations that were made in the course of that development process were ever sold or used for commercial purposes. Thus, the Court concludes that Apotex failed to demonstrate that the exception of

experimental use found in s 55.2(1) of the Act with respect to the disputed lots applies. Consequently, Apotex must be found liable for the infringement of the regulatory material it developed.

F. *Apotex' Defences to Infringement*

[239] In this proceeding, Apotex raises the following defences as to non-infringement on the following basis: (i) limitation period, and (ii) estoppel and abuse of process. As such, it is important to note that Apotex bears the burden of proof as to each of these defences.

(1) The Limitation Period

[240] Apotex asserts that Sanofi is statute-barred from seeking any relief in respect of activities taking place more than two years from the commencement of the action in T-933-09, namely before June 9, 2007. Apotex relies on section 39(1) of the *Federal Courts Act*, RSC 1985, c F-7, which provides default limitation provisions in the event that there is no express limitation provision provided in any other federal statute. This provision, as discussed in more detail later, directs that where the cause of action arises in a province, one applies the laws of prescription and limitation in force in that province.

[241] Thus, because Apotex asserts that the cause of action arose entirely in the province of Ontario, it relies on section 4 of the *Limitations Act* (Ontario), RSO 1990, c L-15, which provides a two-year limitation period.

[242] Apotex further argues that while the current *Patent Act* contains an explicit limitation provision at section 55.01, it cannot be applied in the present case because the transitional provisions relating to this section could arguably be read as excluding from its application actions for infringement of patents issued under the "Old Act".

[243] Pursuant to the transitional provision in section 78.2 of the Act, "any matter" in relation to its validity or infringement falls to be determined under the provisions of the Act as it read immediately before October 1, 1989. Thus, Apotex maintains that such provision is not applicable to the present case because none of those provisions contained a limitation period.

[244] On this basis, Apotex asserts that the provincial limitation period of two years applies so as to bar any claims being asserted in connection with the manufacture and sale of the Apotex clopidogrel that was sold in the U.S. in August 2006 (more than two years before the commencement of Sanofi's action in June 2009).

[245] In response, Sanofi argues that section 55.01 of the *Patent Act*, which provides for a six-year limitation period, should apply. This section reads as follows:

Limitation	Prescription
55.01 No remedy may be awarded for an act of infringement committed more than six years before the commencement of the action for infringement.	**55.01** Tout recours visant un acte de contrefaçon se prescrit à compter de six ans de la commission de celui-ci.

[246] Alternatively, Sanofi claims that subsection 39(2) of the *Federal Courts Act*, which also provides for a six-year limitation period, could also apply because the cause of action arose otherwise than in a province. Subsection 39(1) and 39(2) of the *Federal Courts Act* provide as follows:

Prescription and limitation on proceedings	Prescription - Fait survenu dans une province
39. (1) Except as expressly provided by any other Act, the laws relating to prescription and the limitation of actions in force in a province between subject and subject apply to any proceedings in the Federal Court of Appeal or the Federal Court in respect of any cause of action arising in that province.	**39.** (1) Sauf disposition contraire d'une autre loi, les règles de droit en matière de prescription qui, dans une province, régissent les rapports entre particuliers s'appliquent à toute instance devant la Cour d'appel fédérale ou la Cour fédérale dont le fait générateur est survenu dans cette province.
Prescription and limitation on proceedings in the Court, not in province	Prescription - Fait non survenu dans la province
(2) A proceeding in the Federal Court of Appeal or the Federal Court in respect of a cause of action arising otherwise than in a province shall be taken within six years after the cause of action arose.	(2) Le délai de prescription est de six ans à compter du fait générateur lorsque celui-ci n'est pas survenu dans une province.

[247] Sanofi's position is based on the contention that Apotex' global enterprise in respect of clopidogrel resulting in the infringement of the '777 Patent cannot be said to be confined to a single province. Moreover, Sanofi contends that Apotex arranged for and imported bulk clopidogrel bisulfate from […] and exported clopidogrel bisulphate tablets to numerous countries, including the U.S.

[248] While the current *Patent Act* contains an explicit limitation provision at section 55.01 of the *Patent Act*, the '777 Patent is an "Old Act" patent. Under the transitional provisions in s 78.2 of the Act "any matter" in relation to validity or infringement falls to be determined under the provisions of the Act as it read immediately before October 1, 1989 and none of these provisions contains a limitation period. As emphasized by Apotex, section 55.01 of the *Patent Act* does not apply to an "Old Act" patent and does not therefore apply in the present case. In the present case, the default provisions of section 39 of the *Federal Courts Act* are applicable.

[249] As a result, the Court must now determine if the cause of action took place only in the province of Ontario or if it took place elsewhere. This will allow the Court to establish which of subsection 39(1) or subsection 39(2) applies in the circumstances. The Court recalls that in order for subsection 39(1) of the *Federal Courts Act* to apply, all of the elements of the cause of action must have arisen in the subject province, in this case, Ontario.

[250] In *Apotex Inc. v Pfizer Canada Inc.*, 2004 FC 190, 31 CPR (4th) 143, the Federal Court provided an indication as to what could be considered "otherwise than in a province". It observed at paras 14 and 15 that "both the damages suffered as well as the act that caused the damage must necessarily have arisen in the particular province: *Markevich v. Canada* (2003), 223 D.L.R. (4th) 17, at 35 and 36 (S.C.C.); *Kirkbi A.G. v. Ritvik Holdings Inc.* (2002), 20 C.P.R. (4th) 224 at 284 (F.C.T.D.); *Canada v. Maritime Group (Canada) Inc.* (1995), 185 N.R. 104 at 106 (F.C.A.); *Gingras v. Canada* (1994), 113 D.L.R. (4th) 295 at 319 (F.C.A.)". It further observed that in that case "the proceeding allegedly led to lost sales and the inappropriate continuation of a monopoly in Pfizer's favour throughout Canada, and not within any particular province".

[251] In the present case, Sanofi submits that Apotex arranged for and imported bulk clopidogrel bisulfate from […] and exported clopidogrel bisulphate tablets to numerous countries, including the U.S. Moreover, Sanofi emphasizes that to carry out this enterprise, Apotex employed numerous agents including Apotex Corp, Apotex Australia, Apotex New Zealand, Apotex India and Apotex Pharmachem. In addition, Sanofi points to the fact that Apotex Pharmachem acted as agent for […] for filings in many countries including Hungary, Canada, Australia, New Zealand and the U.S. In support of its position, Sanofi further relies on the testimony of Mr. John Hems, Director of regulatory intelligence at Apotex, who testified about the various agency relationships at issue. The evidence demonstrates that there have been submissions made to different regulatory agencies abroad, including the FDA in the U.S. (Hems, cross T1148-1149, 1161-1162).

[252] Sanofi also relies on the testimony of Mrs. Antoniette Walkom, VP of Quality Assurance and Regulatory Affairs at Apotex Pharmachem, [omitted]:

Q. [omitted]?
A. [omitted].
Q. [omitted]?
A. [omitted].
Q. [omitted]?
A. [omitted].
Q. [omitted]?
A. [omitted].
Q. [omitted]?
A. [omitted].
Q. [omitted]?
A. [omitted].

[253] As previously noted, the evidence before the Court reveals that Apotex arranged for and imported bulk clopidogrel bisulfate from […] and exported clopidogrel bisulfate to numerous countries. This evidence on its own is sufficient to conclude that infringement in this case was not

limited to the confines of a single province and it is well established that importation into Canada of a patented product constitutes infringement (see *Schmeiser*, above, at para 44).

[254] The Court further notes that for customs purposes, the importer is the party who has title to the goods at the time the goods are transported into Canada. In the case at bar, the evidence demonstrates that Apotex represented itself as the "importer" in respect of the goods acquired from […] and as an "exporter" with regards to the international sales.

[255] In addition, the Court also agrees with Sanofi that because […] manufactures exclusively for Apotex and to Apotex' specifications, title in the goods passed once they were in a deliverable state. Indeed, title may pass upon manufacture but passes at the latest at the time of delivery to the first carrier in […] (W. Tetley, Marine Cargo Claims, 4th Ed., Éditions Yvon Blais, 2008, pp. 400-40). In this regard, the Court recalls the cross-examination of Jose Miguel Lazcano Seres, Technical Director at […], who testified about contracts and shipping documents between […] and Apotex. According to Sanofi, the use of the term CIF is a further indication of the passing of title and risk no later than delivery to the first carrier.

[256] It is also relevant that Apotex did not show what became of any remaining goods once the injunction was issued in the U.S. and whether these goods were shipped back to Canada.

[257] Finally, the following additional elements demonstrate that Apotex' activities and the resulting cause of action, in this case, cannot be confined to a single province:

- Apotex conducts business and has places of business in other provinces;

- Pharmachem advertises the sale of clopidogrel on its website which reaches beyond Ontario;
- Apotex entered into agreements and accepted purchase orders in Canada from foreign entities; and
- Apotex has engaged an Indian manufacturer to assist in the manufacture of its product and has shipped bulk API to India.

[258] In light of the foregoing, the Court concludes that the damages suffered as a result of Apotex' infringement cannot be limited to a particular province as the cause of action arose otherwise than in a single province. This proceeding will allegedly lead to lost sales and the inappropriate continuation of a monopoly in Sanofi's favour throughout Canada, and not within any particular province. The factual elements put forward by Sanofi in this regard cannot be considered as purely incidental factors. Thus, subsection 39(2) of the *Federal Courts Act* applies and none of the claims in respect of Apotex' activities are statute barred.

(2) The Settlement Agreements and Estoppel Defence

[259] A further defence raised by Apotex concerns the Settlement Agreements signed in March and May 2006. Assessing the merits of this defence requires an examination of these Settement Agreements.

The Circumstances having led to the Settlement Agreements

[260] The circumstances in which the March and May 2006 Settlement Agreements were reached can be summarized as follows.

[261] On November 21, 2001, Apotex filed an ANDA for Apo-clopidogrel with the U.S. Food and Drug Administration (FDA) and an accompanying certification that the U.S. counterpart to the '777

Patent, U.S. Patent No. 4,487,265 (the ‘265 Patent), was invalid and would not be infringed by the Apo-clopidogrel formulation. Because Apotex was the first generic company to so certify, under U.S. law, it was entitled to sell its drug without other generic competition for 180 days upon receiving approval.

[262] On March 21, 2002, Sanofi/BMS commenced an action against Apotex in the U.S. District Court (File No. 02-CV-2255) for infringement of the ‘265 Patent (the “U.S. Clopidogrel Action”). With the commencement of the U.S. Clopidogrel Action, there was a statutory stay which prohibited the FDA from granting final approval to Apotex’ ANDA before May 17, 2005, unless the U.S. Clopidogrel Action was determined against Sanofi/BMS before that time.

[263] On October 24, 2005, given that the statutory stay had expired and the action had not reached trial, Apotex wrote to Sanofi/BMS to confirm Apotex’ intention to launch immediately upon regulatory approval. In its letter, Apotex also confirmed that it had been investing and continued to invest heavily in production for launch.

[264] On January 20, 2006, the FDA approved Apotex’ ANDA. Around the same time, the parties commenced settlement discussions. The commercial context of these negotiations was explained by Dr. Sherman in his testimony. At the time, the U.S. clopidogrel market for Plavix was worth $4 billion per annum. Accordingly, a launch by Apotex coupled with an adverse ruling as to the validity of the ‘265 Patent put Sanofi/BMS at risk of losing in excess of $25 billion over the remaining life of the ‘265 Patent. From Apotex’ perspective, the risks were significant too: It had already invested significantly in inventory in preparation for launch and, despite having advised

Sanofi of this, no motion for an interlocutory injunction had been brought. A launch at risk by Apotex, coupled with a successful motion for an interlocutory injunction would have the immediate effect of precluding further sales by Apotex, while dissipating the enormous value to Apotex of the one hundred and eighty (180)-day exclusivity period (which period would continue to run despite any interlocutory injunction). Furthermore, if Apotex launched at risk and ultimately lost at trial, it would face the prospect of treble damages that are available under U.S. law.

[265] These factors are significant for the purpose of properly understanding the Settlement Agreements that ultimately ensued. Clearly, both sides faced enormous risks going into the negotiations and clearly each side would be interested in attenuating those risks.

[266] Accordingly, during the initial negotiations, the primary focus of both parties was to conclude a settlement whereby Sanofi/BMS would conserve the value of its unexpired patent for as long as possible while Apotex would defer its one hundred and eighty (180)-day exclusivity until the end of the patent term. This was to be accomplished by a six (6)-month license in favour of Apotex at the end of the patent term.

[267] However, during the negotiations, Sanofi/BMS advised Apotex that they were under consent decrees with the Federal Trade Commission (FTC) and the Attorneys General of some of the states in the U.S. that prevented them from entering into patent settlements without prior approval. As a result of this, Apotex demanded and Sanofi/BMS agreed to concessions to Apotex if the settlement was submitted to the regulators but was not approved by them. The concessions were, first, that, in the event of regulatory denial, Apotex would have a period of time within which to sell off its

inventory (*i.e.* without facing the prospect of a motion for an interlocutory injunction) and, second, that, in the event that the action proceeded to trial with Apotex having launched at risk, Apotex would be guaranteed a profit in respect of its sales by way of an agreement to a fixed level of damages that would be less than Apotex' profits.

The March 2006 Agreement

[268] The March 2006 Agreement was signed on March 17, 2006, wherein Sanofi and Apotex agreed to settle the litigations between them involving the '265 U.S. Patent. The main terms of the agreement were the following:

- that the pending litigations between Apotex and Sanofi be terminated and that Apotex release all claims that it brought or could have brought against Sanofi in connection with these litigations;
- that Apotex be granted an exclusive six-month license under the '265 Patent, effective September 17, 2011, to make, use, import, sell and offer for sale its clopidogrel bisulfate ANDA product in the United States, without the right to grant sub-licenses, provided that Sanofi obtain pediatric exclusivity for the product by March 1, 2011;
- that Apotex' license could be triggered at an earlier date depending on Apotex' sole market exclusivity for clopidogrel bisulfate under 21 U.S.C. § 355(j)(5);
- that Apotex inform Sanofi of any event that could constitute a trigger of every basis on which Apotex would have sole clopidogrel bisulfate under the *Hatch-Waxman Act*, in which case Sanofi could elect to accelerate the effective date of Apotex' license;
- that Apotex pay to Sanofi a royalty of 1% of its net sales on all sales of its clopidogrel bisulfate product in the United States during the period of Apotex' exclusivity;
- that Apotex refrain from selling any clopidogrel product in the United States prior to the date its license under the '265 Patent

became effective; that Sanofi reimburse Apotex for their investment in inventory;

- that Sanofi attempt to obtain a release of any claims that […] could have against Apotex pursuant to the contract signed between […] and Apotex dated June 30, 2000; and

- that Sanofi compensate Apotex in the event that certain minimum annual U.S. sales of Plavix could not be met and the understanding that no other license was to be granted under any other patent owned or controlled by Sanofi.

[269] The parties also agreed that the agreement was subject to a regulatory review and provided for alternate terms in the event of any regulatory denial by the FTC and state Attorneys General.

[270] On or about May 4, 2006, the parties were advised by the state Attorneys General that approval of the March 2006 Agreement was denied.

[271] Notwithstanding the failure to secure regulatory approval, both parties confirmed, by their actions and words, their continuing desire to mitigate their commercial risks as they engaged in further negotiations in an attempt to modify the March 2006 Agreement to deal with the provisions that were understood to be of concern to the regulators.

The May 2006 Agreement

[272] Following further negotiations, the parties signed a second Settlement Agreement dated May 26, 2006, with a number of amendments, including a modification in the damages stipulation from 70% to 50% of Apotex' net sales. Sanofi and Apotex agreed to settle the litigations between them involving the '265 U.S. Patent. The main terms of the agreement were the following:

- that the pending litigations between Apotex and Sanofi be terminated and that Apotex release all claims that it brought or could have brought against Sanofi in connection with these litigations;

- that Apotex be granted a license, under the '265 Patent, effective June 1, 2011 to make, use, import, sell, and offer for sale its clopidogrel bisulfate ANDA product in the United States, without the right to grant sub-licenses; in the event that Sanofi could not obtain pediatric exclusivity for its clopidogrel bisulfate product by March 15, 2011, Apotex' license would become effective on April 1, 2011;

- that in the event that Sanofi launched a drug product other than Plavix (with an antiplatelet aggregation agent as an active ingredient) in the United States prior to the effective date of Apotex' license under the '265 Patent, that Apotex be granted a license under that drug product as well;

- that Apotex' license could be triggered at an earlier date depending on Apotex' sole market exclusivity for clopidogrel bisulfate under 21 U.S.C. § 355(j)(5);

- that Apotex inform Sanofi of any event that could constitute a trigger of every basis on which Apotex would have sole clopidogrel bisulfate under the *Hatch-Waxman Act*, in which case Sanofi could elect to accelerate the effective date of Apotex' license;

- that Apotex refrain from selling any clopidogrel product in the United States prior to the date that its license under the '265 Patent becomes effective;

- that Sanofi reimburse Apotex for their investment in inventory;

- that Sanofi attempt to obtain a release of any claims that […] had against Apotex pursuant to the contract signed between […] and Apotex dated June 30, 2000; with the parties' understanding that no other license was to be granted under any other patent owned or controlled by Sanofi.

[273] Again, the parties also agreed that the agreement was subject to a regulatory review and provided for alternate terms in the event of any regulatory denial by the FTC and state Attorneys

General. As such, regulatory approval was not forthcoming. On or about the end of July 2006, Apotex declared regulatory denial pursuant to paragraph 13 of the May 2006 Agreement.

[274] Apotex accordingly proceeded to launch Apo-clopidogrel in the U.S. on or about August 8, 2006. Sanofi/BMS responded by attempting to obtain a temporary restraining order on August 4, 2006 which was refused by Stein J. of the United States District Court – Southern District of New York – because of the provisions of paragraph 15 of the May 2006 Agreement.

[275] However, Sanofi/BMS was successful in its subsequent attempt to secure a preliminary injunction pending trial on August 31, 2006. After a trial, Justice Stein rendered a judgment upholding the validity of the '265 Patent. In subsequent proceedings, Justice Stein fixed on October 19, 2010 Sanofi/BMS' damages in respect of sales of the U.S. Apo-clopidogrel in the amount of U.S. $442,209,362, which represents 50% of the net sales of the U.S. Apo-clopidogrel. In November 2010, Apotex paid into the Court a net amount of U.S. $556,000,000 in respect of the judgment, plus interest and cost.

The Case at Bar

[276] Apotex submits that Sanofi/BMS is precluded from recovering in respect of any of the U.S. Apo-clopidogrel found to be infringing because of these two agreements and more particularly because of paragraph 14 of the May 2006 Agreement which fixed Sanofi's damages in connection with any sale of the U.S. Apo-clopidogrel at 50% of Apotex' net sales of same. Thus, Apotex claims that subparagraph 14(ii) prevents any further recovery in this case. In other words, Apotex claims that the Settlement Agreements preclude Sanofi/BMS from circumventing the bargain they

struck in March and May 2006 by coming to Canada to sue Apotex and recover a second time for the same Apo-clopidogrel in respect of which they have already secured judgment and payment in the U.S. Apotex' understanding of the Agreement is that the "Liability Exposure Provision" (para 14 ii) of the May 2006 Agreement) expressly precludes any claim outside the U.S. litigation for relief in respect of the U.S. sales of infringing clopidogrel bisulfate.

[277] In contrast, Sanofi argues that this alleged defence on the part of Apotex hinges on the incorrect premise that the U.S. litigation and U.S. Settlement Agreements extend to this action and the '777 Patent. Assessing the merits of this defence requires an examination of the Settlement Agreements between Apotex and Sanofi and their submissions.

[278] Sanofi considers that there is no ambiguity and that the Agreements are clear that they are expressly limited to the U.S. litigation under the U.S. Patent.

[279] Based on the terms of the Settlement Agreements, and in particular the Liability Limitation Provision, the Court is of the view that Apotex is not absolved of any liability arising from the infringement of the '777 Patent. The Court considers that there is no ambiguity in the Settlement Agreements and that the parties' intentions are clear on the face of these Agreements. In the absence of any ambiguity in the terms of a written contract, the parties must be held to the literal meaning of such terms (*Eli Lilly & Co. v Novopharm Ltd*., [1998] 2 SCR 129 at pp 166-167; G.H.L. Fridman, "The Law of Contract in Canada", (Thomson Canada Limited, 2006) at 454).

[280] In the case at bar, there is simply no mention of the words " '777 Patent " or "Canada" in the Settlement Agreements nor can any implied term to this effect be read into the Settlement Agreements, given that they are expressly limited to the U.S. litigation under the '265 U.S. Patent. Indeed, page one of both the Settlement Agreements leaves no room for doubts in this regard:

> Sanofi and Apotex agree to settle the litigations between them involving the U.S. Patent No. 4,847,265. 02CV-2255 and 05CV-3965, on the following terms: […]
>
> (May 2006 U.S. Settlement Agreement
> March 2006 U.S. Settlement Agreement)

[281] Further, the Agreements make explicit references to the '265 Patent (U.S. Patent) whilst remaining void of any explicit reference to the '777 Patent or to Canada (e.g. paras 4 and 14). In the face of such clear and unambiguous references, the Court does not consider it apposite to assess extrinsic evidence on this point (*Eli Lilly v Novopharm*, at para 166).

[282] Whilst Apotex may not be satisfied with the outcome of the Settlement Agreements, it is not open to Apotex to ask the Court to depart from the clear language of these Agreements and to read into them the words " the '777 Patent" or "Canada" into the Agreements. Query: Does Apotex' logic means that Settlement Agreements of March and May 2006 also make implied reference to other patents in other foreign jurisdiction?

[283] The fact that, from Apotex' point of view, the Agreements may produce undesirable effect is not sufficient to allow the Court to decide otherwise (*General Motors of Canada Ltd. v Canada*, 2008 FCA 142, 292 DLR (4th) 331 [*General Motors*]). The Court would add that Apotex, a

sophisticated party in the field of pharmaceutical litigation and negotiations, must be held to the clear terms of the bargain it reached under the Settlement Agreements.

[284] Finally, the Court further recalls that Apotex also raised the defences of estoppel and abuse of process in reference to the Settlement Agreements.

[285] With respect to estoppel, Apotex submits that, under this principle, Sanofi is precluded from pursuing in this action what is, according to Apotex, a second claim for compensation in respect of the very same manufacture and sale of the U.S. APO-clopidogrel.

[286] Moreover, Apotex argues that the monetary judgment in the U.S. Clopidogrel Action was secured on the basis of a contractual arrangement between the parties pursuant to which they stipulated as to what is essentially a factual matter (the measure of Sanofi's "actual damages" in the event of a launch at risk by Apotex in the U.S. and subsequent finding that the '265 Patent was valid and infringed). It follows, says Apotex, that Sanofi would be claiming damages in Canada on the same pills that were sold in the U.S. and were the subject of a damages award by Justice Stein of the United States District Court – Southern District of New York.

[287] Apotex also submits that if Sanofi is able to obtain an accounting of profits, they will be able to recoup the 50% that they negotiated away in the March and May 2006 Agreements. Because Apotex claims to have proceeded to act in reliance of that stipulation, Apotex argues that Sanofi should be estopped from attempting to circumvent that stipulation.

[288] An estoppel defence operates to preclude a party from relitigating the same cause of action twice (*Danyluk v Ainsworth Technologies Inc*., 2001 SCC 44, [2001] 2 SCR 460, at paras 18 and 54). In *Toronto (City) v Canadian Union of Public Employees (C.U.P.E.), Local 79*, 2003 SCC 63, [2003] 3 SCR 77, at para 23, the Supreme Court of Canada held that three (3) preconditions must be met for estoppel to be successfully invoked:

> [23] …(1) the issue must be the same as the one decided in the prior decision; (2) the prior judicial decision must have been final; and (3) the parties to both proceedings must be the same, or their privies (*Danyluk v Ainsworth Tech.*, 2001 SCC 44, [2001] 2 SCR 460, 2001 SCC 44, at para 25, *per* Binnie J.) The final requirement, known as "mutuality", has been largely abandoned in the United States and has been the subject of much academic and judicial debate there as well as in the United Kingdom and, to some extent, in this country. (See G.D. Watson, "Duplicative Litigation: Issue Estoppel, Abuse of Process and the Death of Mutuality" (1990), 69 *Can. Bar. Rev*. 623 at pp. 648-51.) …

[289] *Res judicata* is essentially premised on the notion that a matter has already been adjudged and is founded on the principles that a party shall not be vexed twice for the same complaint and that there is a societal value in the finality and conclusiveness of judicial decisions (see *Angle v Canada (Minister of National Revenue)*, [1975] 2 SCR 248, at para 267; *CPU Options, Inc. v Milton* (2006), 79 OR (3d) 365, at para 15 (SCJ)).

[290] Against this background, the Court is not able to accede to Apotex' alleged estoppel defence because the U.S. litigation and the Agreements simply did not deal with infringement or the validity of the '777 Patent. It is therefore not open for the Court to conclude that the issue is the same as the one decided in the Agreements. The Court accordingly agrees with Sanofi that, where the legal rights upon which a cause of action is based were not adjudicated in the previous proceeding, the estoppel principle does not apply.

[291] Apotex has also raised the issue of abuse of process. In common law, judges have an inherent and residual discretion to prevent an abuse of the Court's process (*CUPE*, above, at para 35). However, the Court has not been convinced that this case boils down to a question of abuse of process. On the basis of the evidence and for the reasons mentioned above, the Court remains unpersuaded that Sanofi is using the courts for an improper use and that the integrity of the court's process is at issue in this case.

[292] Thus, for all of these reasons, the defences raised by Apotex fail.

G. *Conclusion*

[293] Subject to the validity of the patent and the defences that were pleaded by Apotex, there can be no question that Apotex has infringed the claims of the '777 Patent. However, there is no need at this time for the Court to assess and award damages as the Court has found the '777 Patent to be invalid for lack of utility and obviousness. The Court will now proceed to the issue of validity of the '777 Patent.

VII Validity

[294] Section 45 of the *Patent Act* provides that a patentee benefits from a presumption of validity. The burden in this case is on Apotex to convince the Court, on a balance of probabilities, that the '777 Patent is invalid. The question of the validity of the '777 Patent raises, in this case, the following issues:

- overbreadth;
- sufficiency;
- anticipation;
- double patenting; and
- utility.

A. *Overbreadth*

[295] If a claim encompasses more than what the inventor actually accomplished or what the inventor actually disclosed, such a claim is invalid. The claims cannot be broader that the invention disclosed (*Apotex Inc. v Hoffmann-La Roche Ltd.* (FCA), [1989] FCJ No 321, 24 CPR (3d) 289).

[296] On the basis of this principle, Apotex alleges that Claim 6 of the ‘777 Patent is overbroad because it encompasses processes that were not invented.

[297] In order to determine whether Claim 6 of the ‘777 Patent is overbroad, the Court must first look at the claims at issue.

[298] The Court observes that Claim 6 of the ‘777 Patent states the process to obtain clopidogrel. Apotex argues that Claim 6 contains no restriction to a particular resolving agent or solvent. The Court recalls that Claim 6 includes the use of optically active acids and solvents that result in the preparation of substantially pure clopidogrel and its pharmaceutically acceptable salts following the process described in Claim 6 (para 107). The Court therefore cannot agree with Apotex because Claim 6 cannot be dissociated from Claims 7, 8 and 9 (see construction of Claim 6 in section F). The Court cannot therefore agree with Apotex that Sanofi has claimed every possible chiral agent and solvent.

[299] Apotex also alleges the issue of purity and the lack of a purity limitation relating to the dextro-rotatory and the levo-rotatory.

[300] The Court recalls that one of the derivatives claimed in the ‘875 Patent is PCR 4099 which is composed from 50% of dextro-rotatory clopidogrel and 50% levo-rotatory clopidogrel. Hence, Apotex argues that the claims of the ‘777 Patent do not contain a purity limitation. According to Apotex’ submission, it would follow that if someone makes PCR 4099 it would be clopidogrel with a 50% impurity and, as a result, this would fall within the claims of the ‘777 Patent, absent a limitation for purity. Apotex accordingly submits that the specification of the ‘777 Patent does not distinguish in sufficient terms the subject matter of the invention and, for this reason, is thus invalid for overbreadth.

[301] It is significant that no witnesses testified to the fact that the claim is broad enough to encompass PCR 4099. The evidence does not indicate that clopidogrel would encompass the racemate. The disclosure of the ‘777 Patent indicates a purity of at least 96% for the dextro-rotatory enantiomer and at least 98% for the levo-rotatory enantiomer. Moreover, the testimony of Dr. Adger, Dr. Hirsh, and Dr. Byrn further confirms that expert witnesses agree to construe the claim as substantially pure. The Court accordingly cannot find overbreadth in relation to the purity of the claims in the ‘777 Patent.

[302] For all of these reasons, the Court finds that a person skilled in the art would construe the claims of the ‘777 Patent as substantially pure. The Court accordingly concludes that Apotex’ allegations of overbreadth are unfounded.

B *Sufficiency*

[303] "Sufficiency" means that the patent's disclosure meets the requirements set out in section 34 of the *Patent Act.* The specification in the patent application must allow a person skilled in the art to replicate the invention, as claimed.

[304] Apotex alleges that the '777 Patent does not disclose sufficient information for the POSITA to put the invention into practice. Yet, in the case at bar, there was no evidence at trial that supported this position in a substantial manner. The invention exists and it can be put into practice with the information contained within the patent.

[305] In sum, Apotex' allegation of insufficiency is rejected by the Court.

C. *Anticipation*

(1) General Principles

[306] In his decision in *Abbott Laboratories v Canada (Minister of Health)*, 2008 FC 1359, 71 CPR (4^{th}) 237, at para 75, Justice Hughes sets out the legal requirements to be considered for anticipation:

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

> 3. If there is sufficient disclosure, what is disclosed must enable a person skilled in the art to carry out what is disclosed. A certain amount of trial and error experimentation of a kind normally expected may be carried out.
>
> 4. The disclosure when carried out may be done without a person necessarily recognizing what is present or what is happening.
>
> 5. If the claimed invention is directed to a use different from that previously disclosed and enabled then such claimed use is not anticipated. However if the claimed use is the same as the previously disclosed and enabled use, then there is anticipation.
>
> 6. The Court is required to make its determinations as to disclosure and enablement on the usual civil burden of balance and probabilities, and not to any more exacting standard such as quasi-criminal.
>
> 7. If a person carrying out the prior disclosure would infringe the claim then the claim is anticipated.

[307] In the present case, the threshold issue is whether the "publications" presented to the Court can be considered in the anticipation analysis.

[308] The relevant date for anticipation is two (2) years prior to the filing date. The filing date is February 8, 1988 and, therefore, the relevant date for whether prior art can be considered in the anticipation analysis is February 8, 1986. In order for the Court to find anticipation, it needs to look back and see if the invention is disclosed.

[309] Under the Old *Patent Act*, the law of anticipation is based upon the former section 27 of the *Patent Act*. As correctly indicated by Sanofi, under section 27 of the Old Act, the invention must not have been described in any patent or in any publication printed in Canada or in any other country more than two (2) years before the Canadian patent application filing. According to Apotex, subsection 27(1)(*b*) of the Old Act is the provision relevant for the case at bar. Subsection 27(1)(*b*) of the *Old Patent Act* states the following:

27. (1) Subject to this section, any inventor or legal representative of an inventor of an invention that was … (*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 … may, on presentation to the Commissioner of a petition setting out the facts, in this Act, termed the filing in the application, and on compliance with all other requirements of this Act, obtain a patent granting to him an exclusive property in the invention.	**27.** (1) Sous réserve des autres dispositions du présent article, l'auteur de toute invention ou le représentant légal de l'auteur d'une invention peut, sur présentation au commissaire d'une pétition exposant les faits, appelée dans la présente loi le « dépôt de la demande », et en se conformant à toutes les autres prescriptions de la présente loi, obtenir un brevet qui lui accorde l'exclusive propriété d'une invention qui n'était pas : […] *b*) décrite dans un brevet ou dans une publication imprimée au Canada ou dans tout autre pays plus de deux ans avant la présentation de la pétition ci-après mentionnée; […]

[310] Thus, only that which is described in printed publications more than two years before the Canadian filing date can be considered.

[311] In this regard, Apotex alleges that there were several posters and abstracts that "anticipated" the invention in the '777 Patent. In addition, Apotex alleges that the '875 Patent disclosed the invention in the '777 Patent.

(2) The Posters and the Abstracts

[312] A number of exhibits were filed before the Court by Apotex with respect to anticipation of the ‘777 Patent. These exhibits relate to abstracts presented at international conferences as well as posters.

[313] The Court will first address the issue of the posters.

[314] In the case at bar, the evidence overwhelmingly demonstrates that the posters referred to by Apotex were not published in the books of abstracts or in any other publication. Therefore, they do not meet the requirements of subsection 27(1)(*b*) as they do not constitute publications. Dr. Hirsh confirmed that posters would not be in the book of abstracts because an individual will normally bring a poster to a conference meeting. He also testified that posters would not end up in a scientific library. Dr. Sanders agreed that posters were not part of the abstracts. Dr. Colman stated that unless posters were given out, a participant would not have a copy and Dr. Byrn confirmed that posters were not printed. Dr. Shebuski confirmed that abstracts were published but not posters. Dr. Shebuski also added that “as soon as you’re done presenting the poster, you throw it in the trash can and you leave town”. On the basis of this evidence before the Court in the present case, posters are therefore discarded as part of the anticipation analysis.

[315] The Court will now focus on the pertinent published abstracts.

Abstract #1

[316] The first abstract is from Maffrand et al entitled “Animal Pharmacology of PCR 4099, A New Thienopyridine Compound” published in “Thrombosis and Haemostasis” – the Journal of the

International Society of Haemostasis and Thrombosis. It is dated January 10, 1986. Thus, it meets the requirements of subsection 27(1)(*b*).

[317] This abstract makes reference to PCR 4099. It provides the chemical name and indicates that it has been evaluated in rats and baboons. There is mention of three (3) types of thrombosis induced in rats and that PCR 4099 exhibits the same broad spectrum of antiaggregating effect as ticlopidine in animals but it is forty (40) times more potent in rats and ten (10) times in baboons.

[318] It is worthy of note that the abstract does not mention the word “enantiomers” and there is no mention of chirality. There is no compound structure to be found either. There is no drawing in this abstract. There is no information concerning differential activity or differential toxicity. Further, the abstract does not specifically disclose or teach the hydrogen sulfate salt of clopidogrel, or how to obtain the dextro-rotatory enantiomer, or their unique and valuable combination of properties. There is nothing in this abstract that would lead a skilled person in the art to resolve PCR 4099 enantiomers, prepare the hydrogen sulfate salt of clopidogrel, or suspect that it had unique advantages over other salts, the racemate, and the other enantiomer. As noted by Dr. Byrn, and the Court agrees, the comments regarding the potency of PCR 4099 as compared to that of ticlopidine would lead a skilled chemist away from looking for new compounds with unknown properties such as the enantiomers.

[319] Thus, this abstract does not disclose the invention in the ‘777 Patent.

Abstract #2

[320] The second abstract is from Thebault et al entitled "PCR 4099 – A New Thienopyridine Derivative with Potent Anti-Platelet Activity in Man". It is dated July 14, 1985. The abstract does not contain any process information related to the contents of the '777 Patent. It states that the racemate PCR 4099 works well. Again, there is no reference to the specific structure of PCR 4099. The abstract states that PCR 4099 exhibits potent antiplatelet activity in man, provides certain test data and indicates that PCR 4099 was well-tolerated both clinically and biologically. It indicates that further studies are planned in order to assess the dose effect relationship to the compound. The abstract is silent with regard to the salts.

[321] Thus, this abstract does not disclose the invention in the '777 Patent.

Abstract #3

[322] The third abstract, entitled "PCR 4099 – A New Antithrombotic drug – Evaluation of Tolerance and of Pharmacological Activity", is dated June 1986. It is published less than two (2) years prior to the date of filling (February 8, 1988) and cannot be relied upon by the Court for the purposes of anticipation.

(3) The '875 Patent

[323] The Court will now address the '875 Patent in the context of anticipation.

[324] The Court recalls that the '875 Patent was filed in Canada on July 8, 1983 and issued on October 8, 1985.

[325] The ‘875 Patent discloses as part of its general teaching a very broad class of thienopyridine derivatives defined by a general formula. In addition, the ‘875 Patent discloses twenty-one (21) specific compounds within this general formula. Dr. Byrn and Dr. Davies testified that clopidogrel or its bisulfate salt is not one of these compounds. Upon reading the patent, the Court agrees with Dr. Byrn and Dr. Davies that the ‘875 Patent does not disclose a method for preparing any enantiomers nor does it disclose its advantages or the bisulfate salts. The claimed invention of the ‘777 Patent is not disclosed by the ‘875 Patent.

[326] More specifically, the ‘875 Patent does not:

- disclose clopidogrel or any pharmaceutically acceptable salt of clopidogrel of Claim 1;
- disclose the bisulfate salt of clopidogrel of Claim 3;
- disclose any of the specific salts of Claims 2-5;
- disclose the process of Claims 6-9;
- disclose the pharmaceutical compositions of Claim 10-11;
- disclose the beneficial properties of clopidogrel;
- disclose the beneficial properties of the claimed salts of clopidogrel; and
- teach how to make the invention of the ‘777 Patent.

[327] Thus, the ‘875 Patent does not disclose the invention in the ‘777 Patent.

[328] Consequently, on this issue, the Court arrives at the same conclusion as the Supreme Court of Canada’s decision in *Plavix*, at para 41:

> [41] Since the ‘875 patent did not disclose the special advantages of the dextro-rotatory isomer and of its bisulfate salt, as compared to the levo-rotatory isomer or the racemate and their salts, or the other compounds made and tested or otherwise referred to in the ‘875 patent, the invention of the ‘777 patent cannot be said to have been disclosed and therefore it cannot be said to have been anticipated.

[329] In light of the above, it is not necessary to consider enablement since anticipation requires proof of both disclosure and enablement (*Plavix*, para 42).

(4) The Conclusion on Anticipation

[330] Neither the abstracts (Maffrand et al entitled "Animal Pharmacology of PCR 4099, A New Thienopyridine Compound", Thebault et al entitled "PCR 4099 – A New Thienopyridine Derivative with Potent Anti-Platelet Activity in Man") nor the '875 Patent disclose the invention of the '777 Patent. A POSITA would not be able to come up with the invention of the '777 Patent through reliance on any of these documents. The Court accordingly finds that the invention of the '777 Patent was not disclosed and was therefore not anticipated.

D. *Double Patenting*

[331] On the basis of the principle that there can only be one patent for one invention (*Whirlpool*, above, para 63), Apotex alleges that the '777 Patent is invalid upon the basis of double patenting.

[332] In *Whirlpool*, above, the Supreme Court of Canada explained the following in connection with the prohibition against double patenting, at para 63 :

> [63] It is clear that the prohibition against double patenting involves a comparison of the claims rather than the disclosure, because it is the claims that define the monopoly.

[333] In *Plavix*, the Supreme Court of Canada indicated that although *Whirlpool*, above, was not a selection patent case, the above statement applies to selection patents (SCC *Plavix* paras 107-108).

[334] It was further decided in *Plavix* that the claims of the ‘777 Patent and the claims of the ‘875 Patent were not identical or coterminous (SCC *Plavix*, para 101). The compounds claims in the ‘777 Patent are distinct from the compounds claimed in the ‘875 Patent.

[335] No new or convincing evidence has persuaded the Court of Apotex’ allegation that Sanofi engaged in double patenting with the ‘875 Patent and the ‘777 Patent. The allegation of double patenting is thus rejected by the Court.

E. *Utility*

(1) The Lack of Utility

[336] The lack of utility has been raised by Apotex with respect to the venous thrombosis issue which is referred to at page 21 of the ‘777 Patent.

[337] The Court has already found that the promise of the ‘777 Patent does not guarantee a treatment of venous thrombosis. Rather, as concluded earlier by the Court, clopidogrel (the compound) can have a use in the treatment of humans. In that context, the issue of whether venous thrombosis is a treatment guaranteed by the promise as argued by Apotex is irrelevant.

[338] In any event, the Court agrees with Sanofi that this issue did not form part of Apotex’ pleadings. Apotex’ pleadings broadly referred to “humans” but they do not concern any specific mention of a lack of utility argument for venous thrombosis.

(2) The Demonstrated Utility

[339] The next issue to be addressed is whether the ‘777 Patent demonstrates utility in humans. In this regard, there is evidence that a clopidogrel human study entitled P-1062 was conducted by Sanofi for purposes of assessing, among other things, any platelet pharmacological activity. The Court shall accordingly consider whether the human study P-1062 demonstrated the utility of the ‘777 Patent.

[340] The human study P-1062 report provides summary information. It states that the human study P-1062 was a randomized, double-blind study in comparison to placebo with ten (10) healthy volunteers.

[341] As part of the the human study P-1062, each subject was to receive four (4) doses of clopidogrel and one (1) dose of placebo with a seven (7)-day interval free of treatment between two doses. Phase I studies were mainly conducted to determine the doses for Phase II clinical studies, as well as in this case, clinical tolerability and laboratory safety, pharmacological activity (aggregation and bleeding), pharmacokinetic profile and drug analysis.

[342] The human study P-1062 was performed from December 1987 to March 1988. As a result, this study was completed after February 1988 – *i.e.* the date of the filing of the ‘777 Patent. Since the human study P-1062 was a double-blind study, the results would not have been available to Sanofi or to Sanofi’s inventors until the blind was broken, after the end of the study in March 1988.

[343] Dr. Hirsh explained to the Court that in a double-blind study neither the patient – volunteers in this case – nor the investigator know whether the placebo or the drug is administered and which dose of the drug is administered until the study is completed. Upon completion of the study, the blind is broken. When the blind is broken, someone in the statistical department would know whether the volunteer received a placebo or the drug. In the event that the volunteer received the drug, that person in the statistical department would know the dosage administered. This is called the "code" and Dr. Hirsh testified that this "code" would be unknown to the investigators and unknown to anyone else – except one or two people in the statistics department – until the study is over, the code is broken and the results are presented.

[344] The evidence adduced at the trial exposed a number of issues and concerns related to the human study P-1062.

[345] Dr. Sanders and Dr. Levy testified that Sanofi would not likely have known the results of the study until the blind was broken, *i.e*. after February 8, 1988. While Dr. Hirsh stated that it was a question as to whether the blind study had been broken, Dr. Levy mentioned during the trial that the disclosure of parts of the results prior to the completion of the human study P-1062 in March 1988 – *i.e.* after the filing of the '777 Patent – may have breached the protocol and might raise concerns as to the legality of the process. This would impact whether the results were reliable.

[346] Further, Dr. Sanders was of the view that even if the results of the clopidogrel study in humans completed after February 8, 1988 were known to Sanofi by February 8, 1988, the only conclusion that could be drawn was that both compounds were non-toxic at therapeutic doses. There

was no demonstration that the toxicity of clopidogrel in humans was superior (had a better toxicity profile) to the toxicity of PCR 4099 in humans.

[347] The Court also observes that Dr. Maffrand confirmed that the studies were conducted on healthy volunteers as opposed to patients. In that regard, Dr. Levy was of the opinion that the results obtained by Sanofi could not be conclusive. The human study P-1062 had been done mostly on healthy subjects and only on very few patients. Hence, for Dr. Levy, Sanofi lacked information and it was too early in the process to draw any conclusions that would demonstrate utility and the promise of the patent. Dr. Shebuski, an expert for Sanofi, also testified that the data collected by Sanofi beginning in February 1988 might not have been sufficient to draw conclusions with respect to clopidogrel and its activity on humans (Shebuski, T5125-5126):

> Q. In 134, based upon the work you reviewed, what can you say about activity in humans? Had that been established?
> A. No.
> Q. By February 8, 1988?
> A. No.
> Q. What more work would have to be done?
> A. Sanofi was aware of some preliminary data that had been generated prior to February 8, 1988. To continue that development, obviously they would need to expand that data set in humans.
> Q. The expanded data set, why would that be required?
> A. That would be required to gain approval of the drug, demonstrating safety and efficacy with FDA or other regulatory bodies in the EU.

[348] On the basis of the evidence and the testimony of the expert witnesses – Dr. Levy, Dr. Shebuski, Dr. Hirsh – and the testimony of Dr. Maffrand (fact witness), the Court draws the following conclusions:

- the human study P-1062, a double-blind study was started in December 1987 and ended in March 1988;
- the study was performed mostly on healthy volunteers;

- some of the results were known by Sanofi prior to the end of the double-blind study and at the time of the filing of the ‘777 Patent (February 8, 1988);
- the evidence is unclear and a doubt remains as to whether the results obtained by Sanofi in January and February of 1988 - prior to the end of the study in March 1988 - breached the double-blind study protocol; and
- in any event, the expert evidence demonstrates that the early results of the studies obtained by Sanofi did not provide sufficient information to be conclusive.

[349] For all of these reasons, the Court remains unconvinced that the human study P-1062 demonstrated the utility of the ‘777 Patent.

[350] The other issue relevant to the demonstrated utility pertains to Dr. Fréhel (a co-inventor of the ‘777 Patent with Mr. Badorc). This issue is the following: Was Dr. Fréhel informed of the activity in humans before the filing of the ‘777 Patent? Although the Court has already concluded that this issue is not determinative of whether there was demonstrated utility at the time that the patent was filed, this issue was nonetheless the subject of much argument and will be addressed by the Court, particularly in light of the memo related to the January 28, 1988 meeting.

[351] Sanofi argued that Dr. Fréhel was informed of the activity in humans and was thus involved in the decision-making process. In closing arguments, Sanofi alleged that (i) the results of the human study P-1062 were discussed at a meeting held on January 28, 1988, (ii) the minutes of that meeting demonstrate that Dr. Fréhel was present at that meeting as an invitee, (iii) some results were obtained on the human study P-1062 and, while the study was not yet completed and had not fully been analyzed, Sanofi’s view is that inhibition of platelet activation in humans was known and was demonstrated prior to the relevant date, *i.e.* February 8, 1988.

[352] Dr. Fréhel did not testify at trial. Mr. Badorc did not assert any knowledge of the results of the human study P-1062 prior to February 8, 1988. While Dr. Maffrand gave evidence to the effect that Dr. Fréhel was involved in the strategy and was informed of the study (human clinical results), a closer look at the documentary evidence raises serious doubts on the participation and involvement of Dr. Fréhel in a relevant portion of the January 28, 1988 meeting.

[353] More particularly, exhibit D-194, Tab 138, confirms that Dr. Fréhel received the memo related to the January 28, 1988 meeting. Exhibit D-194, Tab 139, relates specifically to the setting up of the January 28 meeting. On the second page there is a list of the invitees for the January 28, 1988 meeting. There were in fact two parts to the January 28, 1988 meeting. The first part of the meeting, meeting A, was held in the morning and related to the mode of action of thienopyridines. The other part of the meeting, meeting B, was held in the afternoon and related to the strategy for phases 2 and 3 of clopidogrel. The names of the participants in the morning meeting appear on List A. The names of the participants attending the afternoon meeting appear on List B.

[354] However, Dr. Fréhel's name does not appear on List B. According to the document, Dr. Fréhel was not an invitee to the afternoon meeting. It therefore appears that, according to the documentary evidence, Dr. Fréhel was not involved in the relevant afternoon meeting where the strategy for phases 2 and 3 of clopidogrel was discussed.

[355] The Court accordingly cannot conclude with certainty that Dr. Fréhel participated in the afternoon meeting held on January 28, 1988, and that he was therefore privy to the information regarding the activity in humans.

[356] For this reason, the Court reiterates that it has not been persuaded that the utility in humans has been demonstrated.

[357] The next step for the Court is to analyze whether the promise for use in humans was soundly predicted (*Wellcome*, below, *Olanzapine*).

(3) The Utility – Sound Prediction

(a) The Promise of the ‘777 Patent

[358] As the Court has found that the utility of the patent was not demonstrated as of the filing date of the ‘777 Patent, the Court must now turn to the issue of whether, as of the filing date, Sanofi had a sound prediction for the invention in the ‘777 Patent.

[359] In *Olanzapine*, the Federal Court of Appeal stated that “the promise of the patent is fundamental to the utility analysis” (para 93). In the case at bar, the Court has already found in that there was an explicit promise for use of the compound in humans.

[360] As such, the utility of the Patent will be measured against that promise (*Olanzapine*, para 76).

[361] The relevant date for sound prediction is the filing date. In this case, the relevant date is February 8, 1988.

[362] The Supreme Court of Canada in *Apotex Inc . et al v Wellcome Foundation Ltd*, 2002 SCC 77, [2002] 4 SCR 153, explained that the doctrine of sound prediction encompasses three (3) components. In order to have a sound prediction, there must be: (i) a factual basis, (ii) a sound line of reasoning, and (iii) proper disclosure.

(b) The Prediction

(i) What is the Utility?

[363] Sanofi argued that the conditions of a selection patent, such as the '777 Patent, apply differently to utility compared with novelty, obviousness and double patenting. More particularly, during final arguments at trial, counsel for Sanofi appeared to infer that the Federal Court of Appeal in *Olanzapine* distinguished utility from the other invalidity allegations in the context of a selection patent. Further, Sanofi argued that the "advantages" of a selection Patent do not apply to the utility analysis. For the purpose of recalling what the Federal Court of Appeal held in *Olanzapine*, the Court sets forth the pertinent paragraphs below:

> [27] …[t]he conditions for a valid selection patent serve to characterize the patent and accordingly inform the analysis for the grounds of validity set out in the Act – novelty, obviousness, sufficiency and utility. …
>
> [28] …It only stands to reason that in undertaking an analysis of novelty, obviousness, sufficiency and utility, one should know the nature of the beast with which one is dealing.
>
> [31] …Rothstein J. incorporated his inquiry regarding the alleged advantages of clopidogrel bilsulfate (Plavix) into his analyses of anticipation, obviousness and double patenting. …
>
> [32] …Of course, as stated by Lilly, obviousness is relevant to the validity of a selection patent and, as Novopharm asserted, so is utility. The notion of selection permeates the entire analysis in relation to each of the grounds of alleged invalidity.

[56] …The invention must be self-evident from the prior art and common general knowledge in order to satisfy the "obvious to try" test.

> [145] In the context of a selection patent, the obviousness analysis considers the species properties of the compound, along with its alleged advantages, as described in the selection patent disclosure, for it is there that the inventiveness of the selection lies.
> …

[75] To establish lack of utility, the alleged infringer must demonstrate "that the invention will not work, either in the sense that it will not operate at all or, more broadly, that it will not do what the specification promises that it will do" …

[76] However, where the specification sets out an explicit "promise", utility will be measured against that promise" …

[78] With respect to selection patents, the inventiveness lies in the making of the selected compound, coupled with its advantage or advantages, over the genus patent. The selection patent must do more, in the sense of providing an advantage or avoiding a disadvantage, than the genus patent. The advantage or the nature of the characteristic possessed by the selection must be stated in the specification in clear terms (*Sanofi*, para. 114). In other words, the selection patent must promise an advantage in the sense that, if the advantage is not promised, the patentee will not be able to rely on the advantage to support the patent's validity.

[81] Ultimately, for the purpose of utility regarding a selection patent, the question to be determined is whether, as of the date of filing, the patentee had sufficient information upon which to base the promise. …

[87] The above-noted inquiries (promise of the patent, information upon which to base the promise and information to soundly predict the promise) are discrete inquiries. Each requires a separate analysis.

[88] …It reiterated its position that the advantages are relevant to obviousness and have no bearing on whether olanzapine meets the utility criteria. …

[90] …I do not accept Lilly's position that the advantages are relevant only to obviousness. …

> [93] I have stated earlier that the promise of the patent is to be ascertained at the outset of analysis with respect to utility. The promise is to be construed by the trial judge within the context of the patent as a whole, through the eyes of the POSITA in relation to the science and information available at the time of filing. The promise of the patent is fundamental to the utility analysis.

[364] Based on the above-quoted paragraphs from the Federal Court of Appeal's reasoning in *Olanzapine*, it is clear that the advantages of a selection patent are relevant to the entire inquiry of patent validity – obviousness, novelty, utility and sufficiency.

[365] In addition, for the '777 selection Patent, the promise of the patent is the utility for which the patent must be measured. As stated by the Federal Court of Appeal in *Olanzapine* at para 87:

> "The above-noted inquiries (promise of the patent, information upon which to base the promise and information to soundly predict the promise) are discrete inquiries. Each requires a separate analysis."
>
> [Emphasis added]

[366] With the above in mind, the Court will now turn to the promise of the patent and how it is applied to the analysis on sound prediction.

(ii) The Promise of the Patent

[367] The promise as construed by the Court is for the use of the invention in humans.

[368] As the invention encompasses a number of advantages, the manner in which the advantages relate to the promise of the patent was a pivotal issue in this case. Hence, the following question: Does the Court consider all of the advantages as a whole in the sound prediction analysis, or does

the Court consider each of the advantages separately when determining whether the inventor had a proper basis for a sound prediction for the promise of the patent?

[369] Apotex argues that each of the advantages must be individually scrutinized for purposes of determining whether there was a sound prediction (*i.e.* the prediction that it was less toxic and more active in humans).

[370] Yet the Federal Court of Appeal in *Olanzapine*, at paras 105-106 and 110-112, cautioned against separately analyzing each specific advantage to the level of the promise of the patent. Apotex' contention to the contrary must accordingly be rejected.

[371] More generally, the issue of the promise of the patent is inextricably linked to Apotex' argument regarding the relative activity and toxicity of clopidogrel. Thus, the Court turns to this next question: How are the advantages of a selection Patent linked to the promise of the Patent?

Advantages vs Promise of the Patent

[372] Apotex contends that the promise of the '777 Patent was for the relative activity and toxicity of clopidogrel in humans. As indicated above, the Court does not consider that each of the advantages of the invention is to be assessed independently but Apotex argues that the '777 Patent promised that each advantage would be substantial. For the reasons stated below, the Court is of the opinion that the '777 Patent does not promise relative activity, toxicity and tolerability compared to the l-clopidogrel or PCR 4099. Rather, the patent only promises that there is a difference.

[373] First, one of Apotex' main arguments is that there is no factual basis or sound line of reasoning for the prediction that clopidogrel was less toxic/better tolerated in humans than PCR 4099 or l-clopidogrel as of February 8, 1988. Apotex refers to Table IV in the '777 Patent in this regard. Apotex contends that Table IV shows that the LD_{50} for the racemate PCR 4099 was 1615, for clopidogrel bisulfate it was 2591, and for the levo-rotatory it was 1702. The range is from highest to lowest calculated at 1.6 and amounts to a range that provides only a slight difference. According to Apotex, a skilled person, based on what is in the patent, would have no reasonable basis of predicting the difference in toxicity between the compounds.

[374] Second, Apotex makes a similar argument with respect to relative activity. For Apotex, the promise is not merely about activity but rather relative activity. This promise is that clopidogrel is at least as active as the racemate PCR 4099, and that the levo-rotatory is inactive or almost inactive. Apotex contends that the promise of the '777 Patent deals with therapeutic administration of the medicine to treat. It follows, according to Apotex, that this is where the promise of comparative activity has to be determined.

[375] Having considered the two (2) arguments above, the Court is of the view that Apotex misses the point. Indeed each advantage described in the '777 Patent is not to be scrutinized on its own, but rather in conjunction with the entire invention as described in the '777 Patent.

[376] In reality, Apotex is asking the Court to reach the very conclusion against which the Federal Court of Appeal warned in the *Olanzapine* decision. The point is that there is one invention and one promise of the patent in the case of the '777 Patent, and the Federal Court of Appeal accordingly

cautioned against separately analyzing each specific advantage referred to in the patent's disclosure. Otherwise, each advantage would be required to reach the level of a promise of the patent. The Federal Court of Appeal indicated that this approach amounted to "putting the cart before the horse" (para 105).

[377] The Federal Court of Appeal explained in *Olanzapine*, at para 106, the following:

> [106] Also of concern in relation to the analysis of each specific advantage is whether the trial judge had an appreciation of the distinction between the promised advantage (if the specific advantage was indeed promised) and the data upon which it is based. *Ranbaxy* addresses this distinction and has been referred to earlier. Finally, the approach taken, in the manner in which it was taken, precludes the possibility that any number of seemingly less significant advantages (when considered separately) may suffice when considered cumulatively, provided that the cumulative advantage is substantial.

[378] If Apotex' line of reasoning were followed, each one of the advantages would not hold up to the standard, and thus there would be no sound prediction.

[379] In particular, if the Court accepted Apotex' argument regarding the method of relative activity, the Court would have to ignore the fact that when the seemingly less significant advantages are considered cumulatively, as in the '777 Patent, there is a substantial advantage.

[380] Likewise, Apotex argues that the '777 Patent promised a substantial difference between the activity, toxicity and tolerability of clopidogrel when compared with l-clopidogrel or PCR 4099.

[381] In this regard, the Court recalls that the promise of the patent, as determined earlier in these reasons, can be described as the use of the invention in humans. And also as explained earlier, the invention of the ‘777 Patent is a compound which is useful in inhibiting platelet aggregation, has greater therapeutic effects and less toxicity than the other compounds of the ‘875 Patent, has the advantages of the salts (crystallizes easily, not hygroscopic and sufficiently water-soluble) and the methods for obtaining that compound.

[382] As the promise of the patent is the use of the invention for treatment in humans, and the invention only specifies “greater” or “lesser” values, the Court will not scrutinize the degree of difference as argued by Apotex, but it will inquire into whether there was a sound prediction that there would be some degree of activity, tolerability and toxicity difference that would occur in humans.

[383] This is similar to the situation in *Servier*, above, where Justice Snider found that the promise of the ‘196 Patent was that all of the compounds claimed would have some level of inhibition. Justice Snider stated at paras 358-359:

> [358] To reiterate my earlier finding, the promise of the ‘196 Patent was that all of the compounds claimed would have some level of ACE inhibition when measured *in vitro* and that some of the compounds would have sufficient activity to treat hypertension and cardiac insufficiency. There was no prediction or promise that all of the compounds of claims 1, 2 and 3 would be capable of treating hypertension or cardiac insufficiency. It follows that there was no prediction that any of the compounds with an all R-configuration on the backbone would necessarily be capable of treating hypertension or cardiac insufficiency.
>
> [359] While admittedly demonstrating that compounds with the R-configuration had a low level of activity as compared to those with the S-configuration, the conclusion I draw from the prior art relied on by

> Apotex is that compounds with the R-configuration at various positions of the backbone would be expected to have some level of ACE inhibition. Indeed, this was not disputed by Apotex's experts, Drs. Marshall, McClelland, and Thorsett, who agreed that some activity was recorded in the prior art when stereoisomers with the R-configuration had been used. For example, in his affidavit, Dr. Thorsett writes:
>
> > By the filing date of the '093 Application... it had been established as part of the common knowledge of the person skilled in the art that certain stereochemical configurations at centers 1-3... namely one or more of them being "R" was readily associated with an extremely poor and non-useful inhibitor activity against ACE in vitro.
> >
> > [Emphasis added]

[384] Thus, the Court will now turn to the factual basis for asserting the activity, tolerability and toxicity differences in animal models. This is the foundation for the prediction that it would have use in humans.

i. ***Information to Base Toxicity and Tolerability Advantages***

[385] The '777 Patent contains LD_{50} results in Table IV. These results are a measure of toxicity and tolerability. Sanofi points out that the results contained in Table IV not only demonstrated a differential LD_{50} and LD_{10} between clopidogrel and the levo-rotatory enantiomer, but also that there were convulsions observed with the levo-rotatory enantiomer. The LD_{50} value is a measure of lethality in the test species after a single administration of the compound.

[386] On this point, Apotex relies on Dr. Sanders' opinion and contends that the LD_{50} test was conducted in female rats and that it is "obsolete", "toxicologically inadequate, and misleading", would have "no place in modern pharmaceutical and chemical research" and would not be at all predictive of a low repeated dose of toxicity in humans. Thus it would not provide the skilled reader

with information about the toxicity that would be expected on administration in the course of treatments of the same compounds to humans. Apotex further argues that the skilled person could not make a prediction regarding the relative toxicity of clopidogrel, PCR 4099 and I-clopidogrel. Finally, Apotex also disputes that clopidogrel has a larger therapeutic index than PCR 4099.

[387] On this issue, the Court heard from two (2) toxicology experts: Dr. Sanders and Dr. Rodricks.

[388] While the Court favoured Dr. Sanders' objective background on toxicology, the Court recalls that the testimony of both Dr. Sanders and Dr. Rodricks revealed a number of discrepancies.

[389] Dr. Sanders admitted in cross-examination to having referred to the number 1550 when the correct number was in fact 155. Furthermore, with respect to production 234, Dr. Sanders referred to the LD as being 1,250 to 5,000 instead of 1,250 to 2,500. The Court does not accept that these differences were insignificant and the Court views these mistakes as more than mere typographical errors. Although the Court is aware that Sanofi translated these reports with the numbers relied on by Dr. Sanders, the fact is that Dr. Sanders relied on incorrect numbers for his opinion. In these circumstances, the reliability of Dr. Sanders' report and testimony were questionable.

[390] Similarly, Dr. Rodricks claimed during cross-examination to have performed a given calculation but failed to provide it in support of his related conclusions. Also disconcerting to the Court was the fact that Dr. Rodricks tendered an expert report in another proceeding, described as the Levaquin Report which reviewed a series of preclinical tests on levofloxacin as well as the

racemate ofloxacin. During cross-examination, it was revealed that Dr. Rodricks borrowed and imported identical paragraphs from the Levaquin Report into his report in the case at bar and hence provided selective information to the Court. Again, the reliability of Dr. Rodricks on this issue is questionable.

[391] Thus, whilst the Court found the testimonies of Dr. Rodricks and Dr. Sanders to be of some assistance on the issue of toxicity, it has given them limited weight.

[392] In terms of persuasive evidence given on this point, the Court notes that a Sanofi study (D-136, Tab-122 – SA361) demonstrated a differential LD_{50} and LD_{10} and that convulsions were a problem with PCR 4099 and the levo-rotatory enantiomer but not with clopidogrel. On this basis, it can be concluded that there was a differential toxicity as well as the better tolerability of clopidogrel.

[393] The Court also notes that Dr. Sanders testified that a comparative toxicity between two (2) compounds could be demonstrated by a two (2)-week repeated dose toxicity study in two (2) species. Such a study was in fact conducted by Sanofi.

[394] In addition, the Court reviewed the numerous previous toxicological studies in different species of both sexes (rat, mouse and baboon) prior to February 8, 1988, including:

(a) acute oral toxicity studies in male and female rats with both enantiomers and racemate (SA361, SA234, SA409, SA388, SA528);
(b) acute oral toxicity studies in male and female mice with both enantiomers and racemate (SA234, SA409, SA528); based upon review of the ‘777 Patent and Sanofi internal reports;

(c) one-week dose ranging study in male and female rats with PCR 4099 (SA236);
(d) two-week oral toxicity study in male and female rats with SR25989C (SA407);
(e) two-week oral dose range finding study in male and female rats with SR25990C (SA404);
(f) two-week oral toxicity study in male and female baboons with SR25989C (SA408);
(g) two-week oral toxicity in male and female baboons with SR25990C (SA526);
(h) one-year toxicity study in male and female baboons with PCR 4099 (SA412);
(i) six-month toxicity study in male and female baboons with PCR 4099 (SA277);
(j) four-week oral toxicity in male and female baboons with PCR 4099 (SA227);
(k) one-week dose range finding study in male and female baboons with PCR 4099 (SA238); and
(l) numerous other toxicology studies on PCR 4099.

[395] On the basis of this evidence, the Court finds that Sanofi has demonstrated the differential toxicity as well as the better tolerability of clopidogrel.

ii. ***Information to Base Activity Advantage***

[396] In connection with the tests performed by Sanofi scientists in order to demonstrate the activity difference between the D and the L enantiomers in animal models, the Court recalls the following comments made by Dr. Hirsh:

Q. Okay, then it describes:
"The enantiomers were synthesized and tested in animals in order to assess their ex vivo antiplatelet activity and antithrombotic activity."
[as read]
That's consistent with your review of the papers?
A. Yes, yes.
Q. Then it says:
"The L enantiomer has no ex vivo antiplatelet activity in rats."[as read]
A. Correct.
Q. Consistent with what you have seen before?

A. Yes.
Q. "And enantiomer D alone has antiplatelet activity and is therefore twice as active as PCR 4099."[as read]
A. That's what it says, yes.
Q. A little bolder than what the patent said?
A. Yes.
Q. But certainly an understanding at the time?
A. That's what they said, yes.
Q. "Enantiomer D alone has antithrombotic properties with dose response in rats."[as read]
And that would have been based on the various antithrombotic testing that had been done?
A. Right.
Q. And it says:
"These results, together with the first results obtained on acute toxicology showing that the inactive L enantiomer toxicity was more marked than the active enantiomer D, probably even more than the racemic, led us to develop active enantiomer, the D enantiomer."[as read]
(Hirsh, T688-690)

[397] Dr. Hirsh further discussed the advantages of the D compared to the L enantiomer and how they were identified:

A. The D has advantages over the L when it comes to activity, yes.
Q. Yes.
And how was that advantage identified?
A. The advantage was identified in three ways. It was identified in the aggregation tests. It was identified in the single model of the screw in the vena cava, and it was identified in the LD-10, 50, 90 studies.
(Hirsh, cross T598)

[398] The Court also observes that the inventors of the '777 Patent made it clear that they had demonstrated the differential activity in rat model. The '777 Patent states:

- The levo-rotatory isomer is inactive and the dextro-rotatory isomer is at least as active as the racemate (page 13).
- The results shown in Table II demonstrate again that only the dextro-rotatory isomer is active whereas the salts have comparable activities (page 15).
- The results which are presented in Table III show that the levo-rotatory isomer is inactive in this test, in contrast to the dextro-rotatory isomer and the racemate (page 17).

[399] Based on the evidence above, the Court accordingly finds that Sanofi has demonstrated the differential activity of clopidogrel.

[400] It follows that Sanofi has established the foundation for the promise of the patent. The Court must now determine whether Sanofi has established a *prima facie* reasonable inference that the invention could be used in humans. To this end, the Court must assess whether there was a *prima facie* reasonable inference of utility.

(iii) *Prima Facie* Reasonable Inference of Utility

[401] The Federal Court of Appeal in *Olanzapine* emphasized that the threshold required to support a line of reasoning is "that a sound prediction requires a *prima facie* reasonable inference of utility" (para 112).

[402] What is a *prima facie* reasonable inference of utility? The answer is evidence which on its face allows it to be reasonable to conclude, based on the facts, that the invention is useful and does what the patent says it will do.

[403] It is thus relevant at this juncture to consider more closely the factual basis underlying the sound prediction/utility.

(c) Factual Basis

(i) Summary of Chronology

[404] The Court will now consider all of the advantages of the invention of the ‘777 Patent as a whole and will determine whether there was a factual basis for the prediction that the invention could be used in humans.

[405] The starting point for this analysis is to assess the chronology of events that lead up to the discovery of clopidogrel bisulfate and the work that was done at Sanofi before the filing date of the ‘777 Patent.

[406] Although there was a substantial amount of evidence presented at trial regarding the “factual basis for the prediction”, a few of the studies that were disclosed in the ‘777 Patent stand out as critical to the foundation, including:

- PCR 4099 was a racemate that was active;
- PCR 4099 was toxic in a one (1) year study of baboons;
- L-clopidogrel is inactive *in vivo*;
- D- clopidogrel is at least as active as the racemate; and
- L-clopidogrel was toxic, but the D was not toxic.

In vitro – Ex vivo – In vivo

[407] Before assessing the work on ticlopidine and PCR 4099, it is helpful to recall that platelet function and aggregation responses can be monitored in a number of ways that are usually referred to as *in vitro*, *ex vivo* or *in vivo*:

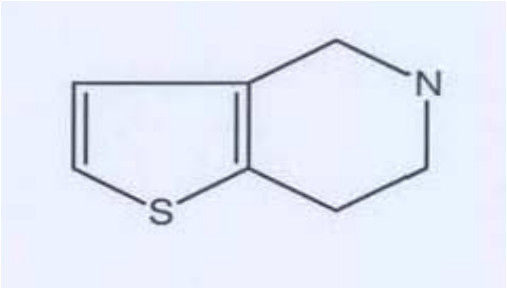
- *In vitro* refers to studying blood platelets from a sample of blood, obtained by venipuncture or other means from a human or an animal, in a test tube;
- *Ex vivo* refers to studying blood platelets from a sample of blood in which the human or animal subject was previously administered an antiplatelet medication; and
- *In vivo* refers to studying platelet function and resulting thrombus formation in a human or an animal model which mimics the thrombotic process which occurs in human beings.

[408] It is also recalled that the ‘777 Patent describes *ex vivo* testing and *in vivo* testing.

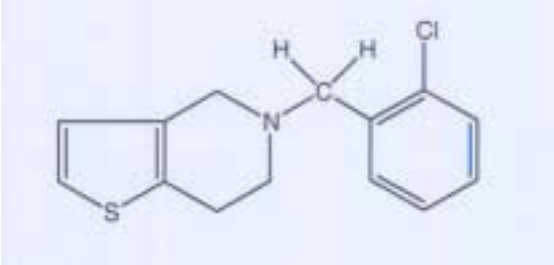
[409] In this case, the Court had the benefit of hearing from Dr. Maffrand, the inventor of the ‘875 genus Patent as well as from Mr. Badorc, a named inventor of the ‘777 Patent. Both testified on the ’777 selection Patent. Dr. Maffrand and Mr. Badorc provided insightful testimony regarding the history and the work conducted by Sanofi that eventually led to clopidogrel. Also, in their final arguments, counsel for Sanofi provided the Court with a very helpful summary of the work conducted by Sanofi in the 1970s and 1980s. This background evidence is relevant to the issue of sound prediction of utility and is accordingly reviewed next.

Ticlopidine

[410] In the early 1970s, Sanofi was conducting research on a class of compounds called thienopyridines. Thienopyridines have a two-ring structure consisting of a five (5) membered ring containing a sulphur atom fused to a six membered ring containing a nitrogen atom:



[411] One of the compounds identified during this research was ticlopidine, which was synthesized in about July 1972. Ticlopidine has the following formula:

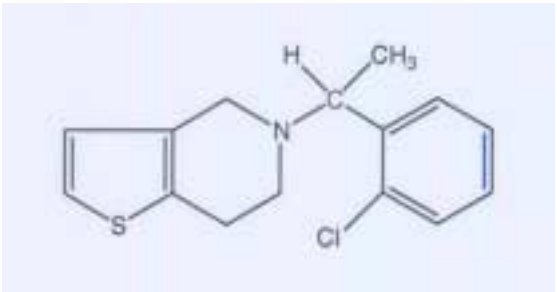


[412] Given ticlopidine's unfavourable side effect profile, there was a need for a drug that was as effective or as more effective than ticlopidine, without the risk of rare but potentially fatal blood disorders. Therefore, Sanofi continued its research on this class of compounds.

[413] While hundreds of racemates were made, Sanofi only worked on separating three (3) racemates: PCR 1033, PCR 3549 and PCR 4099.

PCR 1033

[414] In 1975, the methyl analog of ticlopidine was synthesized, which was referred to as PCR 1033. PCR 1033 has the following formula:



[415] PCR 1033 differs in structure from ticlopidine. Thus, unlike ticlopidine, PCR 1033 is a racemate.

[416] PCR 1033 was tested for antiplatelet aggregation activity and it appeared that PCR 1033 could be considered as a candidate for development as an antiplatelet aggregation agent. However, based on pharmacological studies, the observed toxicity appeared to be worse than that of ticlopidine. Therefore, it was concluded that PCR 1033 was not a good candidate for further development.

PCR 3071 and PCR 3072 – The Enantiomers of PCR 1033

[417] At this point, Dr. Maffrand asked Mr. Badorc to try to obtain the enantiomers of PCR 1033 to see whether the enantiomers of PCR 1033 would have different properties and whether either enantiomer might have a better risk/benefit ratio than PCR 1033.

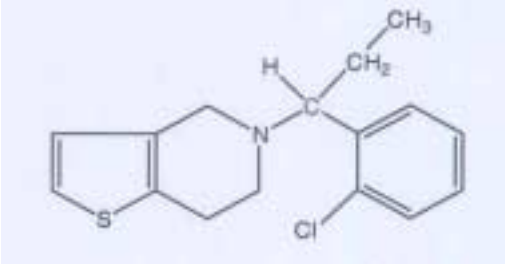
[418] In March 1978, using a technique known as diastereomeric salt formation, Mr. Badorc separated the enantiomers of PCR 1033.

[419] However, testing showed that PCR 3071 exhibited antiplatelet activity while PCR 3072 was inactive.

[420] PCR 3071 was never tested in humans. Based upon the results of toxicology testing, PCR 3071 was tolerated less well than ticlopidine and could not be administered to humans. The decision was made to cease development of PCR 3071.

PCR 3549

[421] In 1978, Mr. Badorc synthesized the ethyl analog of ticlopidine, which was called PCR 3233. PCR 3549 has the following structure:



[422] PCR 3549 differs from ticlopidine in that it is a chiral thienopyridine compound with an ethyl derivative on the bridge carbon. Like PCR 1033, PCR 3549 is a racemate.

[423] Testing conducted by the biological department showed PCR 3549 to be more active than ticlopidine. PCR 3549 was also better tolerated than PCR 1033 but less well tolerated than ticlopidine. Based on an apparently favourable activity/toxicity ratio, Dr. Maffrand formed the view that PCR 3549 should be developed as a drug candidate.

[424] In November 1978, Dr. Maffrand asked Mr. Badorc to separate PCR 3549 into its enantiomers to see if one of the enantiomers had a better risk/benefit ratio.

[425] In April 1979, Mr. Badorc was successful in obtaining the enantiomers of PCR 3549 using the asymmetric synthesis technique.

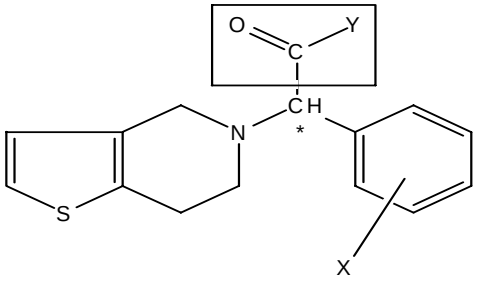
[426] The two enantiomers were sent to the biological department for testing in July 1979. Testing revealed that the enantiomers had platelet aggregation inhibiting activities comparable to the racemate PCR 3549 (see page S277091 of Trial Ex. D-148). In light of this information, Dr. Maffrand made a decision that the development of the enantiomers ought to be abandoned. Dr. Maffrand and his colleagues then focused their efforts on PCR 3549.

[427] It was found that PCR 3549 lacked sufficient therapeutic activity and thus the development of PCR 3549 was abandoned.

[428] After the work on the compounds described above, Dr. Maffrand and his colleagues continued to do research on thienopyridines. Dr. Maffrand explained that the purpose of this research was to find a more potent compound with a better risk/benefit ratio than ticlopidine. Dr. Maffrand hoped to develop a drug that was at least as effective as ticlopidine, with a lower risk of side-effects.

The '875 Genus Patent

[429] Some of the thienopyridine compounds made by Sanofi fell within a distinct genus that was later disclosed in Canadian Patent No. 1,194,875. The general formula in the '875 Patent is as follows:



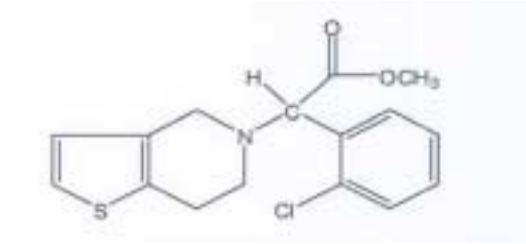
[430] From about 1976, Sanofi decided to synthesize representatives of this class of compounds. Sanofi had previously tested less complex functional groups, such as in PCR 1033 and PCR 3549. Prior to July 13, 1982, Mr. Badorc made at least twenty one (21) of these particular compounds. All were racemates.

[431] In March 1980, Mr. Badorc synthesized the ethyl ester known as PCR 3935.

[432] Based upon the results provided by the biological department, it appeared that PCR 3935 demonstrated good platelet aggregation inhibiting activity.

PCR 4099

[433] In July 1980, Mr. Badorc synthesized the hydrochloride salt of another thienopyridine compound called PCR 4099. The free base of PCR 4099 has the following structure:



[434] The only difference between PCR 3935 and PCR 4099 is that the OCH_3 group is connected to the carbon (marked "C"), as opposed to an OCH_2CH_3 group.

[435] Sanofi's biological department tested PCR 4099 using screening tests, including an antiplatelet aggregation test. Based on these internal results, it was found that (i) PCR 4099 was the most potent thienopyridine compound synthesized to that point of time; and (ii) it was significantly more effective and better tolerated than ticlopidine.

[436] During that time, PCR 4099 underwent further testing. From about July 1980 until about July 1982, seventeen (17) other compounds from the '875 genus were synthesized by Mr. Badorc. All of these twenty-one (21) compounds were later included as examples in the '875 Patent and were tested for activity by Sanofi's biological department.

Decision to Resolve PCR 4099 into its Individual Enantiomers

[437] By 1985, Dr. Maffrand was aware that testing had shown that PCR 4099 had potential negative side effects. Various toxicology studies conducted in 1983 and 1985 had demonstrated the possible tendency of PCR 4099 to cause convulsions in animals at particular dose levels. Further, Dr. Maffrand was still preoccupied with the side effects observed with ticlopidine. With the goal of finding a compound with a better profile than PCR 4099 (and ticlopidine), Dr. Maffrand decided in November 1985 to have the enantiomers of PCR 4099 separated and tested.

[438] Therefore, around November 1985, Dr. Maffrand had a conversation with Dr. Daniel Fréhel in which he told Dr. Fréhel that he would like Mr. Badorc to attempt to separate the enantiomers of PCR 4099.

[439] Further testing was conducted on the enantiomers of PCR 4099, leading to the discovery of clopidogrel bisulfate and the invention of the ‘777 Patent.

[440] The sequence of events is more fully summarized in Appendix C.

(ii) Important Events in Factual Basis

[441] Sanofi had an extensive “track record” that led to the development of clopidogrel bisulfate and the ‘777 Patent. This “track record” provided Sanofi with a factual basis for their prediction that the invention could be used in humans. It is important to highlight its extensive familiarity with the class of compounds leading to the invention, including:

- the work on ticlopidine;
- the work on PCR 4099;
  (i) the one-year study on baboons
- the work on enantiomers of PCR 4099 – d clopidogrel.

(a) *Work on Ticlopidine*

[442] As previously mentioned, ticlopidine is part of a class of compounds called thienopyridines. Ticlopidine was synthesized in or about July 1972. Ticlopidine (Ticlid®) was introduced in France in 1978 and in the U.S. in 1991. However, after ticlopidine was launched in France, it was learned that, when administered to humans, potential fatal blood disorders (neutropenia and thrombotic thrombocytopenic purpura) were associated with it. A number of deaths had been reported to that

effect. Therefore, the work on thienopyridines continued with the objective of finding a drug as effective as ticlopidine but without the risk of fatal blood disorders. This led to the work on PCR 4099.

(b) *Work on PCR 4099*

[443] In July 1980, Mr. Badorc synthesized the hydrochloride salt of another thienopyridine compound called PCR 4099.

[444] During the trial, it became clear that Sanofi had invested significant amounts of time, money and resources to the development of PCR 4099. The following is a list of studies that were performed on PCR 4099 before it was discontinued (Shebuski Report, para 125):

SA No.	Title of Study	Date
SA268	Tolerance and pharmacological activity of single ascending doses	Report date: April 19, 1985
SA273 **SA255**	Tolerance and pharmacological activity of repeated dose	SA273 – Report date: June 28, 1985 SA255 – Report date: September 1984
SA267	Tolerance and pharmacological activity of repeated dose	Report date: April 15, 1985
SA290 **SA292**	Comparison of PCR 4099 (150 mg/day) with Ticlopidine (500 mg/day)	SA290 - Report date: February 10, 1986 SA292 - Report date: February 10, 1986
SA297 **SA306**	Tolerance and pharmacological activity of ascending doses PCR 4099/placebo and Ticlopidine	SA297 - Report date: March 14, 1986 SA306 – Report date: May 29, 1986
SA327	Ascending dose tolerance and efficacy of PCR 4099 in healthy human volunteers	Report date: September 11, 1986

SA291	Pharmacological activity of PCR 4099	Report date: February 10, 1986
SA426	Tolerance and pharmacological activity on thrombocythemic patients	Study completed: June 1987
SA420	Double blind cross-over safety and activity study comparing once daily to twice daily multiple dose treatment of PCR 4099 in healthy volunteers	Study completed: November 1986
SA387	Tolerance and pharmacological activity on haemodialysis patients	Report date: September 4, 1987
SA418	Double blind tolerance and activity study comparing placebo with four dose levels of PCR 4099 in a patient population with peripheral arterial disease	Study completed: May 1987
SA419	Tolerance and pharmacological activity of PCR 4099 administered as a single ascending dose (50/150/300 mg) to healthy volunteers	Study completed: July 1986
SA424	Mechanism of action: study of glycoproteins GP IIb/IIIa	Study completed: May 1987
SA343	Systemic absorption of radiocarbon labelled PCR 4099 after oral intake of a single 150 mg dose in healthy volunteers	Report date: January 23, 1987
SA429	Interaction 4099 and Cimetidine	Study completed: January 1987
SA428	Influence of food intake on Pharmacokinetics of PCR 4099 after a single dose	Study completed: February 1987
SA427	Tolerance and pharmacological activity on thrombocythemic patients	Study completed: September 1987
SA430 **SA391**	Study of PCR 4099 administered with or without antacid medication	SA430 - Study completed: May 1987 SA 391 – Report date: October 10, 1987
SA356	Study of PCR 4099 administered before/after coronary by-pass graft (CABG)	Report date: March 20, 1987
SA423	Study of PCR 4099 administered before and after coronary artery by-pass graft (CABG) vs. Ticlopidine	Study completed: June 1987
SA421	Pharmacological activity and tolerance of PCR 4099 in arteritic patients vs. Ticlopidine	Study completed: September 1987
SA422	Pharmacological activity of PCR 4099 compared with ticlopidine in arteritic patients	Study completed: July 1987

[445] The Court also notes that Dr. Lacheretz took part in and authored numerous studies regarding PCR 4099.

[446] Based on the results yielded by these internal studies, it was found that (i) PCR 4099 was the most potent thienopyridine compound synthesized to that point of time, and, (ii) it was significantly more effective and better tolerated than ticlopidine.

[447] While Mr. Badorc was working on separating the enantiomers of PCR 4099, important work was conducted on PCR 4099. This work included pre-clinical and clinical work and is summarized in the investigational brochure PCR 4099 – An Antithrombotic Agent (Trial Ex. D – 135, Tab 73(a) (SA305). A number of studies using PCR 4099 were performed. The most important and compelling study was the one-year study conducted by Sanofi's toxicology department.

[448] More particularly, a one-year study on baboons produced effects that cannot necessarily be observed with short-term studies, such as a three-month study, and PCR 4099 showed promising potential to be used as a clinical drug.

[449] The one-year toxicity study on baboons started in April 1986 and ended in June 1987. This study was conducted at a low dose of 25, 100 and 400 mg/kg of PCR 4099. In parallel, Sanofi continued to observe convulsions, and the convulsions reached their pinnacle in the one-year toxicity study on baboons (SA412). These studies taken as whole unquestionably demonstrated that convulsions were present and Sanofi concluded that they were due to the toxicity of PCR 4099.

[450] The Court notes that the breadth of experience that Sanofi had regarding the types of short and long-term studies with PCR 4099 added to the factual basis for prediction. The pivotal evidence in this regard was provided by Dr. Lacheretz.

[451] Dr. Lacheretz testified that he was personally and directly involved in numerous studies with PCR 4099, including the one (1)-year study on baboons. At the time of the one (1)-year study, Dr. Lacheretz was working at Sanofi. He left Sanofi the following year. Dr. Lacheretz explained the following:

> […] Bien cette page 17 regroupe les observations quotidiennes, la synthèse des observations quotidiennes réalisée pendant cette étude qui a duré un an. Et ces observations ont révélé l'apparition de crises convulsives dans les trois groupes traités. Encore une fois, on utilise trois niveaux de dose et dans les trois doses utilisées, on a observé des crises convulsives.
>
> […]
>
> […] Au terme de ce programme toxicologique réalisé avec PCR 4099, on constate factuellement que des convulsions sont systématiquement observées et qu'avec la chronicité du traitement, un effet dose est clairement observé également, ce qui conduit à pouvoir imputer ces convulsions directement au produit. Donc l'ensemble du programme est allé vers la confirmation de l'imputabilité de ces convulsions au produit.
>
> (Lacheretz, T3688-3689)

> Page 17 re-groups the daily observations. Some of these are over the one year of the study and these observations indicated a pattern of convulsive crisis in three groups. We have three levels of dosage and in the three doses used there were convulsive crisis.
>
> ...
>
> At the end of this toxicology program for PCR 4099 we observed that convulsions were systematically observed and with the treatment the dosage effect is clearly observed which leads one to be able to impute

> these convulsions to the product. So the overall program did confirm the responsibility of the product.
>
> (Lacheretz, English RD7530)

[452] Based on Dr. Lacheretz' testimony, it is clear that Sanofi concluded that the convulsions were dose-dependent.

[453] As for the testimony provided by the toxicology experts, they both revealed flaws. However, on the issue of the one-year study on baboons, the Court prefers Dr. Rodricks' testimony because it confirms and complements Dr. Lacheretz' testimony. In particular, Dr. Rodricks explained that the baboons could not tolerate the very high doses that were used in shorter term studies. They succumbed early. Dr. Rodricks further explained that the point behind the longer one-year study was to get the material into the animals at a dose that would not cause them to die early or to otherwise be disabled, considering that a one-year study at a lower dose could produce effects that would not necessarily be observed with short-term studies e.g. three (3) months. On that point, in cross-examination, Dr. Sanders testified to the same effect regarding lower dosage.

[454] The results concerning the one-year study in baboons are in a table on which Dr. Rodricks provided the following explanation:

> First of all, you see on the left, they have three different groups of baboons. Then you see in the second column the doses used for each group. So there is a 0, that's the control, 25, 100 and 400, and then the number of animals presenting with seizures.
> So a number of animals in which they saw it, and then they also have the number of seizures. Some animals had more than one seizure during the study. And the importance of the table, we have a general conclusion about convulsions, but what this table tells me as a toxicologist is that you had an increasing rate of convulsions, more of them, as the dose went on.

(Rodricks, T3308-3311)

[455] Dr. Rodricks further opined that the dose-dependent response illustrated by the one-year study indicated that the convulsions were a result of the compound and not a result of the proneness of baboons to convulsions.

[456] In this regard, Apotex argues that the convulsions in baboons at 25 milligrams per kilogram would not be considered important because the baboons were prone to convulsions, and were not considered to be a good model for what would occur in humans in this respect. However, Dr. Lacheretz explained why the baboon was chosen for the studies:

> Le babouin, je le précisais précédemment, l'espèce non rongeur, on a le choix entre le chien, c'est souvent le chien qui est utilisé, le primate non humain, et à l'époque on utilisait des babouins pour des raisons sanitaires et politiques – aujourd'hui, on utilise du macaque –, et la troisième espèce non rongeur qui était possible était le micro porc.
>
> Et généralement, en première intention, le chien était sélectionné. Ce que je me souviens de cette époque, c'est que pour le développement de ticlopidine et pour des dérivés de thiénopyridine, ces produits induisaient des vomissements chez le chien, à des doses assez faibles, ce qui ne rendait pas possible la réalisation des études toxicologiques chez le chien. Il est connu que le chien peut présenter des vomissements assez facilement, un chien peut vomir facilement sans que ce soit d'origine pathologique, et donc c'est parfois une limitation à l'utilisation du chien dans les études de toxicologie. Et l'alternative à cette difficulté est de sélectionner le primate non humain. C'est la raison pour laquelle ces études du PCR 4099 ont conduit à la sélection du babouin.
>
> (Lacheretz, T3682-3683)
>
> Well, as I specified earlier, non-rodent species over the choice between the dog -- and often dogs are used. The non-human primate, at the time we used baboons for sanitary and political reasons. This is no longer the case

> today. We use (foreign word). And the third non-rodent species which was possible was a mini-pig. And usually the dog was chosen first.
>
> What I remember of this time is that for development of ticlopidine and thienopyridine the product induces the vomiting in dogs at fairly low doses which made it impossible to carry out toxicology studies in dogs. It's a known fact that dogs vomit fairly easily. A dog can vomit easily without it being because of pathology so this sometimes placed a limit on the use of dogs in toxicology studies. The alternative to this difficulty is to select the non-human primates and that's why PCR 4099 studies led to the selection of a baboons.
>
> (Lacheretz, English RD7530)

[457] Dr. Lacheretz' testimony unquestionably confirms in the Court's view that the baboon was the most appropriate animal model for the prediction in humans. Based on their previous experience with the dog model in a similar compound, it was the logical choice to use the baboon for study purposes.

[458] Finally, as a result of the one-year study on baboons, Sanofi decided to stop the work on PCR 4099 in April 1987. Significantly, the "Simon Memo" dated April 16, 1987, sent by Mr. Pierre Simon, Director of Research and Development at Sanofi Research, stated that the studies conducted on PCR 4099 would cease allegedly due to convulsions. The Court ruled during trial that this memo was a proper business record under s 30(1) of the *Canada Evidence Act* but that it was cognizant that the memo represents Dr. Simon's beliefs. It was at this point that Sanofi focused their attention on the enantiomers of PCR 4099.

(c) *Work on Enantiomers of PCR 4099*

(i) The '777 Patent: ex vivo Studies

[459] The Court recalls that three (3) tests were performed and the resulting data is reflected in four (4) tables in the ‘777 Patent.

[460] The first test is an *ex vivo* test wherein the activity on the aggregation of platelets was induced by ADP or collagen and then measured by using the well-established Born method. The Court notes the following:

- Tables I (page 14) and II (page 16) of the ‘777 Patent set out the results of the platelet aggregation assays using ADP and collagen, respectively.
- The results shown in Table II demonstrate again that only the dextro-rotatory isomer is active whereas the salts have comparable activities.
- The antithrombotic activity of the compounds was studied in a venous thrombosis test using a screw thread described by T. Kumada et al “Experimental model of venous thrombosis in rats and effect of some agents” (1980) Thrombosis Research 18; 189-203, Exhibit 8. Based on this testing, the ‘777 Patent concludes on page 17 that the levo-rotatory isomer is inactive in this test, in contrast to the dextro-rotatory isomer and the racemate.

(ii) Additional ex vivo Studies

[461] In addition to the *ex vivo* assays set out in the ‘777 Patent, Sanofi also conducted additional *ex vivo* assays which are summarized and explained in Dr. Shebuski’s report at para 86 and following:

a. The *ex vivo* kinetic effect of SR 25990C on ADP-induced platelet aggregation was studied in female rats (n=5) administered SR 25990C at oral doses of 2.5 and 10 mg/kg (SA414, page 8; SA111, pages S05135-S05148). SR 25990C was only modestly effective at the low dose (2.5 mg/kg) whereas at the higher dose (10 mg/kg), SR 25990C started to show an impairment of platelet aggregation at 0.5 hr post oral administration with the maximal effect occurring at around 6 hrs post-treatment. By 72 hrs, the platelet aggregation responses had still not returned to the baseline control responses.

b. Similarly, the *ex vivo* kinetic effect of SR 25990C on collagen-induced platelet aggregation velocity was studied in female rats (n=5) administered SR 25990C at oral doses of 2.5 and 10 mg/kg (SA414, page 9; SA111, pages S05135-S05148). SR 25990C was only modestly effective at the low dose (2.5 mg/kg) whereas at the higher dose (10 mg/kg), SR 25990C started to show an impairment of platelet aggregation velocity at 0.5 hr post oral administration with the maximal effect occurring at around 6 hrs post-treatment. By 72 hrs, the platelet aggregation responses had still not returned to the baseline control responses owing to the irreversible nature of this inhibitor.

c. The *ex vivo* effect of SR 25990C on ADP-induced platelet aggregation was evaluated at 2 hrs post-administration of SR 25990C orally at single doses of 1.25, 2.5, 5.0 or 10 mg/kg in male and female rats (n=5 each). Ticlopidine was also evaluated at a dose of 100 mg/kg, p.o. (SA414, page 10; SA110, pages S05035-S05052; SA111, pages S05089-S05095). The 2.5 mg/kg dose of SR 25990C was modestly effective with the most inhibition (approx. 75% or greater) observed at the 10 mg/kg dose in females and 20mg/kg in males. Ticlopidine, at the 100 mg/kg dose, was relatively ineffective, at the dose administered in this test, compared to SR 25990C.

d. Similarly, the *ex vivo* effect of SR 25990C on collagen-induced platelet aggregation velocity was evaluated at 2 hrs post-administration of SR 25990C orally at single doses of 1.25, 2.5, 5.0 or 10 mg/kg in female rats and 2.5, 5, 10 and 20 mg/kg in male rats (n=5 each). Ticlopidine was also evaluated at a dose of 100 mg/kg, p.o. (SA414, page 11; SA110, pages S05035-S05052; SA111, pages S05089-S05095). The 2.5 mg/kg dose of SR 25990C was modestly effective with the most inhibition (approx. 75% or greater) observed at the 10 mg/kg dose in female rats. In male rats, the 20 mg/kg dose of SR 25990C was more inhibitory than the 10 mg/kg dose. Male rats appeared to require a slightly higher dose of SR 25990C than female rats to attenuate collagen-induced platelet aggregation velocity to a similar degree. Ticlopidine, at the 100 mg/kg dose, was relatively ineffective, at the dose administered in this test, compared to SR 25990C in both female and male rats.

e. The *ex vivo* effect of SR 25990C on thrombin-induced platelet aggregation was also evaluated at single oral doses of 1.25, 2.5, 5 and 10 mg/kg in female rats (n=5) and 2.5, 5, 10 and 20 mg/kg in male rats (n=5). Ticlopidine was also evaluated at a dose of

100 mg/kg, p.o. (SA414, page 12; SA111, pages S05098-S05102; SA131 pages S05218-S05220) to female and male rats (n=5 each). The 5 mg/kg dose of SR 25990C was highly effective against thrombin-induced platelet aggregation with the most inhibition (approx. 90% or greater) observed at the 10 mg/kg dose in female rats. In male rats, the 20 mg/kg dose of SR 25990C was similarly effective to the 10 mg/kg dose in female rats. Ticlopidine, at the 100 mg/kg dose, was relatively ineffective, at the dose administered in this test, compared to SR 25990C in both female and male rats.

f. The effectiveness of single oral doses of SR 25990C on ADP-induced *ex vivo* platelet aggregation in rats (n=5) was evaluated when the compound was administered either p.o. or intraduodenal (i.d.) in doses of 2.5, 5 and 10 mg/kg (SA414, page 13; SA111, pages S05123-S05126, S05167-S05168). The intraduodenal route, at all doses studied, was more effective than the p.o. dosing regimen to attenuate ADP-induced platelet aggregation.

g. Biliary and pancreatic secretions, in the antiaggregatory (ADP) effect of SR 25990C after intraduodenal administration, were evaluated in rats (SA414, pages 14-15; SA137, pages S057539-S057555). Animals treated with SR 25990C with a biliary shunt had profoundly more inhibition of ADP-induced platelet aggregation compared to those animals with a water shunt.

h. The effect of SR 25990C on *ex vivo* ADP-induced platelet aggregation was studied in rats following 4 different routes of administration; p.o., i.v., i.p., and i.d. (SA414, page 16; SA110, pages S05035-S05052; SA111, pages S05161-S05166; SA111, pages S05131-S05134). Doses of SR 25990C ranged from 1.25 to 100 mg/kg. At a dose of SR 25990C of 5 mg/kg, p.o., ADP-induced aggregation was attenuated by approx. 60% or greater with profound inhibition at 10 mg/kg, p.o. Administration of SR 25990C by the i.v. route, inhibited ADP-induced aggregation as well but to a slightly lesser extent at comparable doses to the p.o. route. Dosing of SR 25990C by the i.p. route was effective at 10 mg/kg and the s.c. route was highly ineffective, even in doses up to 100 mg/kg, indicating greater bioavailability following i.d. vs. p.o. routes of administration. However, intraduodenal dosing is not a normal means of drug administration applicable to therapeutic drug commercialization.

i. Evaluation of the onset of action of SR 25990C in rats after oral or intravenous administration revealed that the onset, to attenuate

ADP-induced platelet aggregation, was similar by either route (SA414, page 17; SA111, pages S05135-S05141, S05157-S05160). Furthermore, the *ex vivo* antiaggregatory (ADP) effect of SR 25990C after i.v. administration (10 mg/kg) is independent of re-absorption of the biliary secreted compound or metabolites in the rat (SA 414, page 18; SA137, pages S057552-S057553).

j. Additional rat studies examined the platelet binding dependency of SR 25990C to inhibit ADP-induced *ex vivo* platelet aggregation (SA414, page 21; SA110, pages S05062-S05067). Rat platelets incubated in plasma treated with SR 25990C were not inhibited. Platelet aggregation was inhibited profoundly when platelets were treated with SR 25990C followed by incubation with SR 25990C-treated or -untreated plasma. These data indicate that the activity of SR 25990C is exclusively associated with platelets.

k. Dose-related effects of three days repeat oral administration to female and male rats (n=5 each) of SR 25990C, on ADP-induced *ex vivo* platelet aggregation, revealed that as the dose of SR 25990C was elevated from 0.625 to 5 mg/kg/day for 3 consecutive days, that progressively more platelet aggregation inhibition resulted (SA414, pages 22-23; SA111, pages S05108-S05112, S05113-S05117). The maximal effect occurred at 3 days post dosing of 5 mg/kg, p.o. Female rat platelets appeared to be a bit more sensitive to SR 25990C than male rat platelets. Ticlopidine was also assessed for its antiaggregatory effect in these studies as well in separate animals (n=5 female and male rats each). Ticlopidine was moderately effective in females as an inhibitor of ADP-induced *ex vivo* platelet aggregation at the dose administered.

l. Similarly, dose-related effects of three days repeat oral administration to female and male rats (n=5 each) of SR 25990C, on collagen-induced *ex vivo* platelet aggregation velocity, revealed that as the dose of SR 25990C was elevated from 0.625 to 5 mg/kg/day for 3 consecutive days, that progressively more platelet aggregation inhibition resulted (SA414, pages 24-25; SA111, pages S05108-S05112, S05113-S05117). The maximal effect occurred at 3 days post dosing of 5 mg/kg, p.o. As in the previous study, female rat platelets appeared to be a bit more sensitive to SR 25990C than male rat platelets. Ticlopidine was assessed for its antiaggregatory effect in these studies as well in separate animals (n=5 female and male rats each), and was a relatively ineffective inhibitor of collagen-

induced *ex vivo* platelet aggregation velocity, at the dose administered.

m. Dose-related effects of three days repeat oral administration to female and male rats (n=5 each) of SR 25990C, on thrombin-induced *ex vivo* platelet aggregation, revealed that the lowest dose of SR 25990C evaluated (0.625 mg/kg/day for 3 consecutive days) was highly effective in inhibiting thrombin-induced *ex vivo* platelet aggregation (SA414, pages 26-27; SA131, pages S05221-S05224, S05225-S05228). Female rat platelets appeared to be highly more sensitive to SR 25990C in terms of inhibiting thrombin-induced platelet aggregation than male rat platelets. Ticlopidine was assessed for its antiaggregatory effect in these studies as well in separate animals (n=5 female and male rats each), and was a relatively effective inhibitor of thrombin-induced *ex vivo* platelet aggregation, but not to the degree achieved with SR 25990C.

n. A similar study to that above, in which the thrombin platelet stimulating concentration was elevated from 0.1 U/ml to 1.0 U/ml (a ten-fold increase) revealed that the inhibition seen in the previous study was now completely reversed by the higher concentration of thrombin such that SR 25990C was completely ineffective (SA414, page 28; SA131, pages S05225-S05228). Thus, higher concentrations of thrombin can overcome SR 25990C-induced platelet inhibition, however the physiological relevance of these data is not apparent.

o. *Ex vivo* platelet aggregation responses to ADP were also evaluated following *in vivo* administration to rats (n=5) of combinations of the levo-rotatory hydrogen sulfate salt isomer (SR 25989C) with the dextro-rotatory hydrogen sulfate salt isomer (SR 25990C) (SA414, page 30; SA111, pages S05169-S05178). SR 25989C did not interfere with the pharmacological platelet inhibition achieved with SR 25990C (5 mg/kg) at doses of SR 25989C up to 50 mg/kg.

p. Female rat bleeding time (n=5) was assessed following single oral administration of SR 25990C in doses ranging from of 1.25 to 20 mg/kg (SA414, page 44; SA73, pages S05522-S05523). Bleeding time, as assessed by tail transection, increased in a dose-dependent manner in response to SR 25990C in all animals. The maximal effect on bleeding time occurred at 10 mg/kg, p.o. Elevation of bleeding time is an expected result when utilizing antiplatelet agents. However, excessive elevation

of bleeding time is a safety concern and may require adjustments to dosage amount and frequency of administration.

q. SR 25990C was also evaluated on inhibition by ADP of PGE_1-activated adenylate cyclase in rat and rabbit platelets. In the rat study (SA414, pages 64-65) and the rabbit study (SA414, pages 66-67), SR 25990C at doses of 25 mg/kg, p.o. and 50 mg/kg, p.o., respectively, neutralized the inhibition by ADP of PGE_1 activated platelet adenylate cyclase.

[462] Each of the above studies referred to Sanofi's factual basis.

(iii) The '777 Patent in vivo Studies

[463] The '777 Patent also describes one of the *in vivo* studies conducted by Sanofi to assess the antithrombotic activity of the compounds. The study described in the '777 Patent is the test of venous thrombosis on a screw thread described in Toshihiko Kumada et al, "Experimental model of venous thrombosis in rats and effect of some agents" (1980), Thrombosis Research 18; 189-203, Exhibit 8.

[464] In this connection, Dr. Shebuski testified that while the model referred to above is primarily focused on venous thrombosis, it also provides information on the platelet inhibiting activity of a compound (Gheslain Defreyn et al, *Pharmacology of Ticlopidine: A Review* (1989), Seminars in Thrombosis and Hemostatis 15; 159-166 at 163-164, Exhibit 15; J.M. Herbert et al, *Clopidogrel, A Novel Antiplatelet and Antithrombotic Agent* (1993), Cardiovascular Drug Review 11; 180, Exhibit 16; H. Gerhard Vogel & Wolfgang H. Vobel, eds., *Drug Discovery and Evaluation: Pharmacological Assays* (Berlin Heidelberg: Springer-Verlag, 1997) ch B: *Activity on blood constituents* at 162, Exhibit 9).

[465] The efficacy of SR 25990C to prevent venous thrombosis was demonstrated in the rat model described above (female rats, n=10/group). The results presented in Table III of the '777 Patent (page 18) demonstrate that SR 25990C is effective in the dose range of 5-10 mg/kg, p.o. to prevent thrombus formation *in vivo* as is SR 25990E. The racemate (PCR 4099) is similarly effective. The levo-rotatory hydrogen sulfate salt isomer, SR 25989C is inactive in preventing thrombus formation in the rat.

(iv) Additionnal *in vivo* Studies

[466] In addition to the animal model described above, Sanofi also tested the compounds in other animal models and in particular the arterio-venous (A-V) shunt model and the stasis induced thrombosis model. This testing is also summarized and explained in Dr. Shebuski's report at para 104 and following:

- The A-V shunt or extracorporeal model is a surgical model in which an artery is connected to a vein to provide a new conduit for arterial blood to flow through. A silk thread is placed in the conduit to elicit thrombus formation. This method was reported in T. Umetsu & K. Sanai (1978) "Effect of 1-methyl-2-mercapto-5-(3-pyridyl)-imidazole (KC-6141), an antiaggregating compound, on experimental thrombosis in rats" Thromb. Haemost. 39: 74, Exhibit 17. (Shebuski Report, para 105)

- The A-V shunt model has also been suggested to be predictive of the utility of substances which can be used in extracorporeal circuits in humans (R.A. Shand et al. (1984) "Expression of the platelet procoagulant activity *in vivo* in thrombus formation in an extracorporeal shunt in the rat" Thromb. Res. 36: 223, Exhibit 19). (Shebuski Report, para 108)

- SR 25990C was evaluated in the rat (female rats, n=5/group) A-V shunt model. Single oral dosing of 1.25 to 20 mg/kg, p.o. resulted in dose-dependent inhibition of thrombus formation in the animal model with the effective dose of SR

25990C being between 2.5-5 mg/kg, p.o. (SA414, page 48; SA113, pages S05197-S05199). The effectiveness of SR 25990C was also demonstrated using this model in the male rat, at single oral doses of 5-20 mg/kg, p.o. (SA113, pages S05194-S05195). (Shebuski Report, para 109)

- Stasis-induced venous thrombosis can be achieved by simply ligating a vein for a period of time. Upon release of the ligation, blood flow does not return due to the presence of an occlusive thrombus. This method was described by I. Reyers et al. (1980) "Failure of aspirin at different doses to modify experimental thrombosis in rats" Thromb. Res. 18: 669, Exhibit 21). (Shebuski Report, para 110)

- Evaluation of SR 25990C in another model of venous thrombosis (ligation of the inferior vena cava in female rats, n=10/group) provided similar efficacy results, in the same dose-range, (SA414, pages 54-55; SA89, pages S05565-S05571) to the A-V shunt and wire coil models described above. (Shebuski Report, para 111)

[467] Cumulatively, all of the studies described above constitute a positive track-record. These tests demonstrated the following:

- L-clopidogrel is inactive *in vivo*;
- D- clopidogrel is at least as active as the racemate; and
- L-clopidogrel was toxic, but the D was not toxic.

(iii) Draw-Backs in Factual Basis

[468] The factual basis for Sanofi's prediction that the invention under the '777 Patent could be used in humans must, according to Apotex, be considered in light of both positive and negative findings. Regarding the latter, Apotex referred to:

- the "set-backs" that Sanofi encountered with PCR 3549 and PCR 5235. Both of these compounds were "active" in animals and "inactive" in humans; and
- the convulsions in baboons.

[469] The Court will address each of the above in turn.

a) *PCR 3549 and PCR 5325*

[470] Apotex alleges that Sanofi was not forthright regarding its "negative" track-record in the development of the compounds leading to clopidogrel bisulfate. In particular, Apotex points to two (2) compounds that were originally active in animals but that were then later found to be inactive in humans. Apotex argues that, because there was evidence to suggest that the enantiomers of PCR 4099 may not be active in humans, there was no sound prediction that the activity seen in animals with respect to clopidogrel bisulfate would translate to humans.

[471] Dr. Maffrand, in his evidence, indicated that there were experiments conducted with two other compounds: PCR 3549 and PCR 5325. He acknowledged during cross-examination that both of these compounds were active in animals but inactive in humans.

[472] Cross-examination also revealed that Dr. Shebuski, whom the Court recalls is one of Sanofi's witnesses, was not aware of compounds PCR 3549 and PCR 5325.

[473] The Court agrees with Apotex that Sanofi's finding with respect to PCR 3549 and PCR 5325 represent a "draw-back" in the factual basis. However, the Court is of the view that the existence of a "draw-back" in the thienopyridine class of compounds does not substantially detract from the previously-described positive track record that Sanofi had otherwise established.

b) *Convulsions and Baboons*

[474] Apotex argues that many of the results obtained by Sanofi regarding convulsions were not due to the toxicity of PCR 4099 but were due solely to the proneness of baboons to convulsions. Hence, for Apotex, PCR 4099 was not toxic and there were no serious grounds to stop its development in favour of the dextro-rotatory enantiomer.

[475] Dr. Sanders and Dr. Rodricks provided opinions on the matter of convulsions and baboons.

[476] The question regarding convulsions and baboons is the following: Are the baboons so prone to convulsions that a toxicologist would not have been concerned about the toxicity of either PCR 4099 or clopidogrel to the point he would rule out convulsions in a one-year study at doses as low as 25 mg/kg?

[477] While it is true that the record shows that Sanofi's scientists and toxicologists provided comments in studies that baboons may be prone to seizures, Dr. Hirsh, an expert for Apotex, was of the view that baboons were a good model for toxicology testing. In reality, the evidence, when considered as a whole, does not allow the conclusion that convulsions or seizures in baboons were in no way related to PCR 4099. The Court has difficulty accepting the suggestion that a practicing toxicologist would not consider such convulsions pertinent to an evaluation of human safety and would merely ignore them. While scientists are aware that baboons are species particularly sensitive to convulsions, the evidence does not demonstrate that baboons are of no value in scientific study. If this were the case, studies would never be conducted on baboons. The convulsions and the study results would *ipso facto* be ignored.

[478] Turning to Sanofi's six-month study on baboons, Apotex emphasizes that the convulsions in the six (6)-month study were not considered to be significant. Apotex points to the following comment regarding the six (6)-month study on baboons – PCR 4099 at page 15:

> These seizures could not definitely be attributed to PCR 4099 considering the proneness of baboons to this kind of reactions (already observed in previous studies).

[479] The Court considers that the above-quoted comment does not definitively rule out the link between the convulsions and PCR 4099. As explained by Dr. Lacheretz, who was responsible for the toxicological studies from the time of the administration *in vivo* until the autopsy, the above-quoted comment cannot be interpreted as a definitive statement. Dr. Rodricks also provided the same explanation.

[480] Further, Dr. Lacheretz explained that the proneness of baboons to experience convulsions does not have the same impact on short-term studies as long-term ones. Moreover, the cumulative number of studies conducted by Sanofi between 1983 and 1987 make it less likely to conclude that the convulsions are necessarily linked to the proneness of baboons and Dr. Rodricks' explanation echoed Dr. Lacheretz':

> A. And if you look at those results, you see that the number of animals having seizures increases with increasing dose. That's what I'm talking about.
> Q. Okay.
> A. I think they were talking about when in the course of the treatment did the doses occur. So they saw no pattern. In other words, a high dose may have caused a convulsion late, a low dose may have caused it earlier. There was no particular pattern of when it occurred in an individual animal. But what's important is the finding in 3.1.1 on page 18 which shows the total number of events, whenever they occurred, goes up with dose. <u>So that's what I meant in my report when I said this is dose related effect and the spontaneous rate – the explanation that it</u>

> was just a spontaneous occurrence in the baboon is – no longer holds when you have data like this. When the dose goes up, you get more and more events, you have to believe this is due to the drug at this point.
>
> [Emphasis added]
>
> (Rodricks, T3582)

[481] Thus, the Court agrees with both Dr. Lacharetz and Dr. Rodricks that, on a balance of probabilities, it is more likely than not that the convulsions were due to the drug PCR 4099 and not due to the proneness of baboons to convulsions contrary to Apotex' assertion.

[482] Therefore, the Court does not agree that convulsions in baboons were a factor that substantially detracted from the positive track record that Sanofi had otherwise established.

(iv) Conclusion on Factual Basis

[483] Sanofi obtained results in short-term and long-term studies to support its conclusion that there was a factual basis for its prediction that the invention could be used in humans.

[484] There were important milestones leading to the conclusion that, before the filing date, Sanofi had a sound factual basis established by hundreds of studies performed on ticlopidine, PCR 4099, and clopidogrel. These studies led to the following:

- Work on Ticlopidine;
- PCR 4099 was a racemate that was active in animal and human models;
- PCR 4099 was toxic in a one-year study of baboons;
- L-clopidogrel was inactive;
- D-clopidogrel was at least as active as the racemate;
- L-clopidogrel was toxic, but the D was not toxic.

[485] The Court is cognizant of the fact that “draw-backs” have been raised by Apotex. However, these “draw-backs” fall short of convincing the Court that the evidence, considered as a whole, does not provide a *prima facie* factual basis allowing Sanofi to conclude as it did. Although there was much debate as to whether baboons are prone to convulsions or not, the evidence is not conclusive to the effect that the convulsions were a direct result of Sanofi having chosen the baboons as an animal model. The observed convulsions might have various causes. The choice of the baboon could be central to the occurrence of convulsions but, again, it might not be. There is simply no conclusive evidence on this point.

[486] Relying on the evidence, the Court therefore finds that (i) the length of the one-year study from April 1986 to June 1987 on baboons, (ii) the low dosage of 25 mg/kg and, (iii) the number of acute toxicity studies conducted between 1983 and 1987 – when read as a whole – provided Sanofi with the factual basis to conclude that convulsions were observed in animals receiving PCR 4099 and the levo-rotatory enantiomer but that no convulsions were observed in animals receiving clopidogrel.

[487] In addition, although there was evidence that Sanofi had tested a compound that was active in animals and then inactive in humans, this finding is not strong enough to negate the substantial track record established by Sanofi when weighed against all of the other information that Sanofi possessed at the time of filing.

[488] In sum, the Court concludes that there was a factual basis for the prediction that the invention would have a use in the treatment of humans.

(d) Sound Line of Reasoning

[489] Now, the Court must turn to the question of whether there was a sound line of reasoning that would link the factual basis to the prediction (*Eli Lilly Canada Inc. v Novopharm Ltd.*, 2011 FC 1288, [2011] FCJ No 1571).

[490] As Justice Hughes recalled in *Pfizer Canada Inc. v Mylan Pharmaceuticals ULC,* 2011 FC 547, [2011] FCJ No 686, at para 242: "[t]hat the line of reasoning is not required to be a "certainty", as long as it is "*prima facie* reasonable" ".

[491] For purposes of determining whether there was a sound line of reasoning, in the case at bar, the Court must consider the following elements that would provide the Sanofi scientists with that line of reasoning:

(i) Knowledge of stereochemistry
(ii) Knowledge of toxicology
(iii) Knowledge of haematology
(iv) Knowledge of pharmacology
(v) Knowledge of previous work on thienopyridine compounds
(vi) Knowledge of extrapolation from animals to humans.

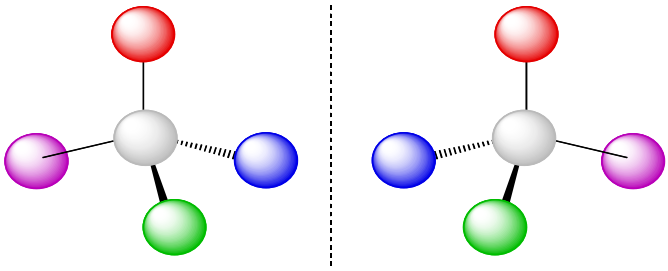
(i) Stereochemistry

[492] Dr. Davies provided the Court with thorough and insightful testimony on chemistry and stereochemistry. The relevant portions of his evidence, as set forth in his Expert Report, are reviewed next (Davies Report, para 25-44, 53-59).

[493] Starting from first principles, molecules (including drugs) are composed of atoms. Atoms form molecules by precise connectivity rules. These rules involve the joining of atoms by chemical

bonds, which are represented by a straight line (—). Most chemical bonds are formed when atoms share electrons between them.

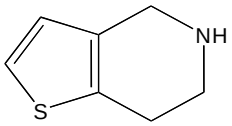
[494] Following the connectivity rules, carbon atoms can bond to four (4) other atoms. If a carbon atom forms four bonds with four different atoms (these four (4) separate units are represented by different atom connectivities), then there are two (2) possible spatial orientations of these groups. In the drawing below, a solid wedge depicts an atom or group oriented toward the viewer, and a hashed wedge depicts an atom or group oriented away from the viewer:



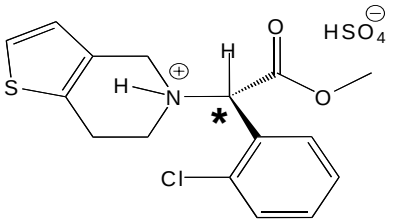
[495] Although these molecules have the same connectivity, they are non-superimposable mirror images. This means that, no matter how much you twist or turn these molecules, you cannot make one identical to the other without breaking and rearranging the bond connectivities. Such molecules are called “enantiomers”.

[496] Chemists characterise each enantiomer in a given pair of enantiomers based on the spatial arrangement, or configuration, of the atoms around the stereogenic carbon atom using the symbols “(*S*)” and “(*R*).” These designations refer to the absolute configuration (the actual arrangement in 3D space) based on a standard nomenclature convention.

[497] Turning to clopidogrel bisulfate, it belongs to a general class of compounds known as "thienopyridines," named for the bicyclic ring structure containing sulfur (S) and nitrogen (N) atoms shown below:

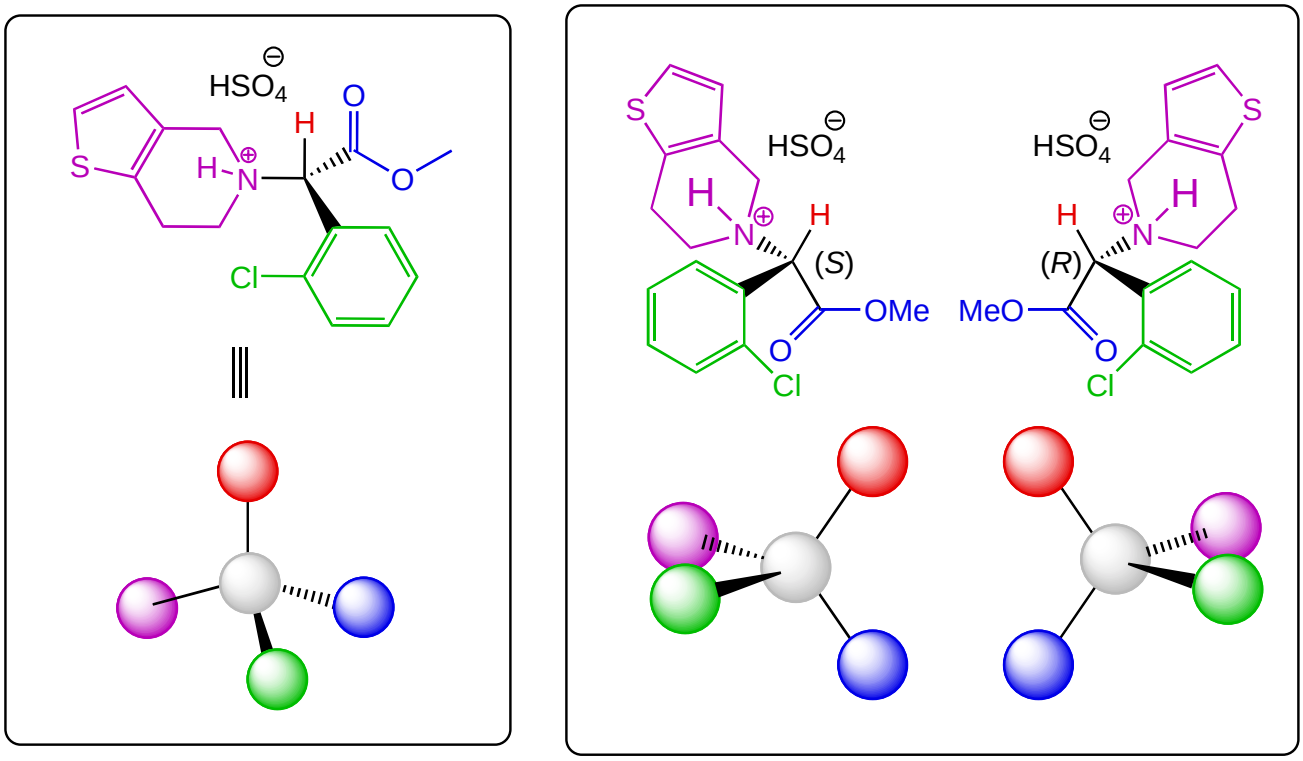


[498] Clopidogrel bisulfate itself has the following chemical structure:



[499] The carbon atom marked with an asterisk (*) is the stereogenic carbon atom. The clopidogrel molecule has the (*S*)-configuration, and in a methanol solution, rotates polarized light to the right, thus it is called the dextro-rotatory enantiomer. The HSO_4^- indicates the bisulfate portion of the salt molecule.

[500] In the next figure below, clopidogrel bisulfate is shown on the left, and is compared to its corresponding levo-rotatory enantiomer on the right:



[501] A critical aspect of Sanofi's sound line of reasoning was its understanding of the structure and stereochemical relationship of clopidogrel bisulfate to the previous compounds that had been synthesized and tested by Sanofi, including PCR 4099 and ticlopidine.

(ii) Toxicology

[502] Both Dr. Sanders and Dr. Rodricks provided the Court with background information with respect to toxicology. While the background information provided by Dr. Rodricks addressed the issue of toxicity, the Court found it to be overly broad and general. The Court found the background information provided by Dr. Sanders to be more instructive. Dr. Sanders has a Masters in Pharmacology, is a Doctor of Veterinary Science and has a Ph.D. in toxicology. The relevant portions of his evidence, as set forth in his Expert Report, are reviewed next (Sanders Report, page 11-15).

[503] Toxicology is a branch of biology and medicine concerned with the study of the adverse effects of chemicals on living organisms. It is the study of symptoms, mechanisms, treatments and detection of poisoning.

[504] Dr. Sanders referred to Dr. Loomis and noted that "toxicity of a given compound can be distinctly different within members of a species or between species if the suitable enzymatic systems between the test organisms are not identical" (Sanders Report, page 15).

[505] Toxicological tests are used to define the toxicological response in a test subject to a compound in the very specific conditions of the test. Typically, pre-clinical toxicological tests are conducted *in vitro* and in multiple animal systems in a large range of conditions. In the pharmaceutical industry, the results of all of these pre-clinical tests are compiled and analyzed to arrive at a toxicity profile of the candidate drug under the conditions of the pre-clinical test. This profile is then used to design the clinical trials to determine if and how the drug can be given to humans and at a level that will be safe so that the effects of the compound in humans can then be studied.

[506] The Court observes that a critical aspect of Sanofi's sound line of reasoning was its understanding of the toxicological relationship and the potential to use pre-clinical toxicity tests to predict clinical toxicity.

(iii) Haematology

[507] Both Dr. Hirsh and Dr. Shebuski were accepted by the Court as experts in haematology. However, the Court preferred the background information provided by the former as opposed to the latter. Indeed, while Dr. Shebuski opined on haematology, many papers he referred to were provided to him by counsel, and many of these papers were never before cited by him in his own publications. The Court therefore found the background information on haematology provided by Dr. Hirsh to be more compelling. The relevant portion of his evidence, as set forth in his Expert Report, is reviewed next (Hirsh Report, para 17, 54).

[508] Hemostasis and thrombosis represent two extreme ends of a spectrum. Hemostasis is a vital physiological process that is geared to prevent excessive blood loss when a blood vessel is punctured. It acts to retain the fluid nature of blood while ensuring that blood remains within the blood vessels.

[509] Platelets are anucleate blood cells that are key components of normal hemostasis, both in ensuring the integrity of blood vessels and aiding in the process of blood coagulation. They are present in all mammals, but each animal species has distinctive platelet characteristics, which are heterogeneous among different species.

[510] Platelets are important participants in arterial thrombosis by virtue of their capacity to adhere to damaged blood vessels and to clump at sites of injury.

[511] When an injury to the vessels occurs, fluid blood is converted into a solid thrombus mass made up of fibrin and blood cells.

[512] Arterial thrombosis is the formation of a thrombus within the arteries. The most important factor in arterial thrombosis is platelets, which undergo adhesion, activation and then aggregation as a result of vascular wall injury.

[513] Venous thrombosis is the formation of a thrombus within the veins. Under normal circumstances, blood flow in leg veins is maintained by contraction of calf muscles during walking and other activities. Most venous thrombi occur in leg veins in regions of sluggish blood flow if there is an additional stimulus to blood coagulation.

[514] It was known by February 1987 that while antiplatelet drugs may reduce the risk of arterial thrombosis (but not venous thrombosis or disorders due to extracorporeal blood circuits), this effect cannot be dissociated from an increased risk of bleeding. Effective treatment must balance antiplatelet inhibition with risk of bleeding.

[515] In addition to the information above, a critical aspect of Sanofi's sound line of reasoning was its understanding of the following haematology relationships:

- ADP was known to be involved in the activation of the platelet; and
- ADP is common to all species.

[516] Dr. Hirsh explained to the Court that ADP was known, before the filing date, to be involved in the activity of platelets (Hirsh, T511):

Q. Okay. And ADP was known to be involved in the activation of the platelet?
A. Well, you mean in this context or
Q. Generally.
A. Generally, ADP was known to be involved in platelet activation, yes.

[517] In addition, Dr. Hirsh confirmed that ADP is common to all species:

Q. "ADP is a general platelet agonist and induces the basic reaction in all mammalian species studied to date."[as read]
A. Right.
Q. True statement?
A. I think it is, yes.
Q. So ADP is common to rats, mice, baboons, humans?
A. When you say "common", you mean that it is produced by them. Yes.

(Hirsh, cross T705-706)

(iv) Pharmacology

[518] Pharmacology raises the three following issues:

- Threshold issue: Is pharmacokinetics relevant?
- What is pharmacology? How does pharmacokinetics relate to pharmacology?
- What do we know about metabolism of clopidogrel and how would POSITA know that metabolism is relevant to clopidogrel?

Threshold Issue: Is Pharmacokinetics Relevant?

[519] During the trial, a dispute arose over whether Apotex could raise the issue of "metabolism" with its experts.

[520] A pivotal moment arose during the trial when Dr. Maffrand, a leader of Sanofi at the time of the '777 Patent, acknowledged during cross-examination that issues of metabolism were important to the '777 Patent. Indeed, Dr. Maffrand knew that primary metabolite "majoritaire" of PCR 4099 was inactive (Maffrand, T4936). But most importantly, in an affidavit filed before an Australian

Court in a case related to the ‘777 Patent, Dr. Maffrand indicated that he had no way of predicting what the activity of either enantiomer would be, or how well-tolerated either enantiomer would be, even if they could be separated. Dr. Maffrand admitted that he lacked the ability to predict the results because he did not know the structure of the active metabolite. In other words, he did not know what would be the interaction between the metabolites and the targets:

> Q. You should still have before you, Dr. Maffrand, the Australian affidavit. It’s a single document, not bound.
> R. Oui... Non, j’ai dit oui...
> Oui, je l’ai.
> Q. I want to ask you to turn to paragraph 158 of this affidavit. It reads as follows:
>
> “I was also aware, based on my knowledge as a chemist, of the risk that even if Mr. Badorc was able to separate the enantiomers of PCR 4099, the individual enantiomer might transform back into the racemic mixture in the body. This was because the presence of the ester function in PCR 4099 could cause the same effect, in the body, as I outlined in paragraph 157 above. I had no way of predicting what the activity of either enantiomer would be, or how well tolerated either enantiomer would be, even if they could be separated. I had no ability to predict these results because I did not know:
> (a) the structure of the active metabolite;
> (b) the actual target receptors in the body these compounds acted on to produce desired and undesired activities; and
> (c) the interactions between the metabolites and the targets.”
>
> You gave that evidence under oath in Australia, did you?
> R. Oui, j’ai fait la déclaration sous serment. Je ne sais pas si...
>
> (Maffrand, T4932-4933)

> Q. You should still have before you, Dr. Maffrand, the Australian affidavit. It’s a single document, not bound.
> A. I have it now.
> Q. I want to ask you to turn to paragraph 158 of this affidavit. It reads as follows:
>
> “I was also aware, based on my knowledge as a chemist, of the risk that even if Mr. Badorc was able to separate the enantiomers of PCR 4099, the individual enantiomer might transform back into the racemic mixture in the body. This was because the presence of the ester function in PCR 4099 could cause the same effect, in the body,

> as I outlined in paragraph 157 above. I had no way of predicting what the activity of either enantiomer would be, or how well tolerated either enantiomer would be, even if they could be separated. I had no ability to predict these results because I did not know:
> (a) the structure of the active metabolite;
> (b) the actual target receptors in the body these compounds acted on to produce desired and undesired activities; and
> (c) the interactions between the metabolites and the targets."
>
> You gave that evidence under oath in Australia, did you?
>
> A. Yes, I stated this under oath.
>
> (Maffrand, English RD7535)

[521] Dr. Maffrand acknowledged that he provided this evidence under oath in Australia. Before the Court at trial he seemed uncomfortable with his Australian evidence and finally indicated that "he did not agree with himself anymore". Nonetheless, the exchange between Dr. Maffrand and counsel for Apotex left the Court with the understanding that the metabolite issue had its importance to the '777 Patent and could be relevant in the equation.

[522] Thus, the issue of pharmacology, and more importantly metabolism, needs to be addressed by the Court.

What is pharmacology? How does pharmacokinetics relate to pharmacology?

[523] Dr. Levy provided the Court with a comprehensive understanding of pharmacology and the relevant portions of his expert report are reproduced below.

[524] The following definitions were provided:

- **Pharmacology** is the study of the effects of chemical agents of therapeutic value or with potential toxicity on biological

systems. It includes the disciplines of pharmacodynamics and pharmacokinetics.

- **Pharmacodynamics** is the study of the molecular, biochemical, and physiological effects of drugs on the body, including their mechanisms of action.

- **Pharmacokinetics** is the study of the time course of drug absorption, distribution, metabolism and excretion (ADME) and the relationship of these processes to the time course and the extent of pharmacological effects, therapeutic and toxic.

[525] There are basic processes that control drug exposure in animals or in humans. Dr. Hirsh, Dr. Sanders and Dr. Shebuski all made references to pharmacology. However, Dr. Levy provided the Court with an understanding of the process that controls drug exposure in animals or humans since drug exposure will determine its effect. This process is known as ADME (absorption, distribution, metabolism, and elimination).

[526] Generally speaking, absorption relates the rate and extent to which a pharmaceutical compound enters the body; distribution relates to the way in which the compound is then spread throughout the body; metabolism relates to the way the body acts on the compound to change the compound and produce metabolites; and elimination relates to the rate and extent to which the compound is removed from the body (Levy Report, para 35-83).

[527] Drug metabolism (also called biotransformation) specifically results from the effects of enzymes commonly located in the smooth endoplasmic reticulum of hepatocytes. Metabolic reactions are varied including oxidation, conjugation, reduction, and hydrolysis.

What do we know about the metabolism of clopidogrel and how would POSITA know that metabolism is relevant to clopidogrel?

[528] Before turning to the discussion on the issue of metabolism, it is important to emphasize that clopidogrel is a pro-drug as opposed to an active drug.

[529] Both Dr. Levy and Dr. Shebuski testified in that respect. They explained that a pro-drug is a chemical as it exists before it is administered. It is not active and needs to be transformed. The pro-drug will be transformed – *i.e.* metabolized – when administered and will then become active. Basically, it will become another chemical.

[530] Dr. Levy explained that there are different types of pro-drugs. Some pro-drugs are hydrolyzed chemically in the gastro-intestinal (GI) tract, others in the GI membrane, and others in the liver. If a drug is unstable in the GI tract, it becomes a source of variability between individuals and thus becomes a source of variability**.** Because the pro-drug must form something else, Dr. Levy explained that "we are at the mercy of how that process is affected. When a drug is active by itself, we are only at the mercy of it dissolving and being absorbed". Hence, the compound would need to be metabolized in order to work (Levy, T2134-2137).

[531] Both Dr. Levy and Dr. Shebuski also indicated that the data of some of the tables in the '777 Patent, namely Tables I and II, were *ex vivo* data. In order to be metabolized, the compound would need to be administered into the blood of the animal (rodent).

[532] The pharmacokinetic/pharmacodynamic relationship is important in order to understand the role between a drug and a metabolite. In essence, drugs can be divided into three categories.

[533] The first group encompasses most drugs. The administered drug will produce the desired effect and all the metabolites are just means of elimination. The second group of drug encompasses a minority of drugs and produces metabolites. The metabolites are active. Hence, the metabolites act and the drug acts. Finally, in rare cases, there is the third group. This is where the drug itself doesn't act and relies completely on the metabolite. Dr. Levy testified that clopidrogrel falls in the third category. Its formation of metabolites was essential in order to understand its activity. This "third metabolite" is three steps removed. Dr. Levy explained that it automatically creates an "unbreachable fire wall" and, thus, any prediction from animal to human is unknown.

[534] In terms of the line of reasoning, Apotex argues that each of the compounds is itself inactive and needs to be metabolized. The consequence of the need to have metabolism in the body is the following: the relative activity of the compounds will depend upon how they are treated by the body (*i.e.* when the active metabolite is formed, how it gets distributed). In other words, the ADME (absorption, distribution, metabolism and elimination) becomes relevant to these compounds and their relative activity.

[535] Apotex accordingly submits that the prediction relates to the relative activity of compounds – the dextro-rotatory enantiomer and the levo-rotatory enantiomer. For example, the dextro-rotatory enantiomer versus the combination, the racemic. These are compounds which differ in spatial orientation and which will perform pharmaceutically dependent on that spatial orientation related to the prediction of stereospecific pharmacokinetics across different species. The '777 Patent provides rat data and makes the promise across species that the stereospecific pharmacokinetics observed in

the rat will be necessarily observed in humans. Apotex argues that this is a prediction without substance on the evidence and that there is no question that the compounds have to be transformed – *i.e.* they have to be metabolized – in order to work.

[536] Apotex further argues that the activity of the compounds depends on ADME and, therefore, the predictivity of the activity depends on the predictivity of ADME across different species. Also, Apotex alleges that ADME is species-specific and that the evidence supports the conclusion that the way compounds are metabolized in the rat is not predictive of how the compounds will be metabolized in humans. Consequently, it is difficult to predict relative potency.

[537] Sanofi did not provide a substantive counter-argument on this exact issue but disagreed and argued that metabolites are not needed to pass regulatory hurdles for new drugs. However, Sanofi did suggest that, even if metabolism was relevant, there is evidence to show that a laboratory rat and a human absorb and eliminate many chemicals in a similar manner (The Laboratory Rat, Baker, 1980 – exhibit D117 H).

[538] The issue as raised by Apotex' contention is thus the following: In the case of human toxicity, short of doing tests on humans, is it sufficient to have done a rat test to know the different and distinct genetic functionalities, the bodily structures and the enzymes?

[539] While there was some divergence between the experts on this issue, it is important to understand the predictability of the animal models in order to appreciate the line of reasoning. As

the Court recalled earlier, it is not required that the line of reasoning be a "certainty" provided it is *prima facie*.

[540] However, Apotex' submissions seemed more akin to "certainty" as opposed to *prima facie*. In providing their testimony, certain experts also lost sight of this distinction. For instance, Dr. Levy testified that he was looking for a reasonable conclusion and later agreed that this represents much more than an inference (Levy, cross T2200). In doing so, the Court is of the view that Dr. Levy provided his testimony with a higher threshold in mind (*i.e.* certainty) as opposed to the legal requirement (*prima facie*).

[541] The Court finds that, based on the evidence, there is no question that a pro-drug compound like clopidogrel has to be metabolized. It was thus critical for Sanofi's scientists to recognize that metabolism was a significant hurdle in the line of reasoning to predict that the invention could be used in humans.

[542] Indeed, in the case at bar, the compound clopidogrel did not stand on its own. It has a history and a background. As explained below, clopidogrel was part of a line of thienopyridine compounds – ticlopidine and PCR 4099. Hence, on the basis on the evidence adduced at trial, it is relevant to assess the previous work from Sanofi on thienopyridine compounds, more particularly ticlopidine and PCR 4099. Sanofi referred to that work as the "track record". This prior work is crucial in order to determine later whether the extrapolation from animal to humans is sound. Sanofi's prior work on ticlopidine and PCR 4099 cannot be divorced from the '777 Patent and must be addressed.

(v) Previous Work on Thienopyridine Compounds

Ticlopidine

[543] As mentioned earlier, ticlopidine was discovered in 1972, introduced in France in 1978 and then introduced in the US in 1991. The experts' testimony confirmed that ticlopidine was tested on both animals and humans.

[544] The antiaggregatory effect of ticlopidine was established in *ex vivo* studies very similar to the methods used with PCR 4099 in humans. Furthermore, the antithrombotic efficacy of ticlopidine was evaluated in humans based on dose-response studies that had been performed earlier in animal models of thrombosis (Thebault et al "Effects of ticlopidine, a new platelet aggregation inhibitor in man" (1975) (Clin. Pharmacol. Ther. 18: 485).

[545] However, because it was discovered in 1985, 1986, and 1987 that ticlopidine had side effects, there was a need for a drug that could be administered in lower doses at which side effects did not materialize. There was a need for another antiplatelet drug (Hirsh, cross T543).

[546] This led to the work on PCR 4099.

PCR 4099

[547] As discussed earlier in these reasons regarding the factual basis, Sanofi performed a large number of studies on PCR 4099. These studies were summarized in an exhibit to Dr. Shebuski's expert report and are attached as Appendix B to these reasons.

[548] In addition, Sanofi's scientists produced a number of investigative brochures regarding PCR 4099.

1) *Investigational Brochure for PCR 4099 (May 1986)*

[549] The investigational brochure dated May 28, 1986 entitled "Investigational Brochure of PCR 4099 – an Antithrombotic Agent" stated that "[i]t is generally accepted that platelets have a pivotal role in the formation of the arterial thrombus. Hence, it has been assumed that a drug which prevented platelet adhesion or aggregation would also prevent thrombosis". Dr. Hirsh accepted that this was a reasonable working theory.

2) *Investigational Brochure for PCR 4099 (January 1987)*

[550] The investigational brochure dated January 1987 is also of interest. It is entitled "Investigational Brochure of PCR 4099 – an Antithrombotic Agent" and consists of the third edition. It states that PCR 4099 is at least ten (10) times more potent than the parent compound, ticlopidine. It is much more powerful (ten fold) than aspirin, while being also effective on animal models on which aspirin itself is inactive.

Summary of Previous Work on Thienopyridine Compounds

[551] In 1988, Sanofi had significant internal knowledge regarding PCR 4099. It had been tested on animals and on humans, and PCR 4099 demonstrated a high antiaggregating effect in rats (and in baboons). Also, Sanofi had conducted similar animal testing with PCR 4099 as with clopidogrel.

[552] In light of the above, the Court cannot but conclude that the previous work conducted by Sanofi on ticlopidine, PCR 4099 and clopidogrel was extensive.

[553] The Court further recalls that Dr. Hirsh recognized that the similarity of the compounds allowed for an extrapolation. Likewise, Dr. Shebuski testified that the pre-clinical studies with PCR 4099 and with ticlopidine that had been conducted on rats were highly predictive of clinical efficacy in humans. The evidence demonstrates that the compounds had a similar structure and metabolism, and the Court is of the view that a POSITA would expect that clopidogrel would have the same mechanism of action. In cross-examination, Dr. Hirsh opined:

> Q. Okay, but what that abstract seems to tell us is that the mechanism of ticlopidine and PCR 4099 appear to be very similar?
> A. Yes, and I would expect that.
> Q. They were both thienopyridines?
> A. Correct.
> Q. And that allows you to do a little bit of correlation or triangulation, I am not sure the best word for that. If you see a similar effect in similar, structurally similar compounds, it's easier to make an extrapolation?
> A. I think it is, yes.
>
> (Hirsh, cross T573-574)

[554] Thus, a critical aspect of Sanofi's sound line of reasoning was its understanding of history with other thienopyridine compounds. This provided Sanofi with a track record of information that could be compared and contrasted with the invention in the '777 Patent.

[555] With this in mind, the Court now turns to the following question: Was there a sound line of reasoning in the extrapolation from animals to humans?

(vi) Extrapolation from Animals to Humans

Value of Animal Testing

[556] However trite on the issue of the value of animal testing, the Court observes that millions of dollars are spent by pharma companies on research using animals. While it can generally be said that animals have some value in science, there was some divergence between the experts with respect to the level of predictability for animal models. The overarching issue is therefore not so much the value of animal testing (the experts were in agreement in that regard) but rather its inference to humans. The issue is to what extent extrapolation from animals to humans is reliable.

[557] For instance, Dr. Levy opined that based on the animal results in ticlopidine, it was reasonable to infer that it had potential use in humans. Dr. Hirsh and Dr. Sanders agreed that a correlation had been established between the animal models and ticlopidine and PCR 4099. More specifically, Dr. Shebuski indicated that animal models of platelet-mediated thrombosis are extremely useful in preclinical studies to determine the safety and efficacy of antiplatelet medications (Paul Didisheim, "Animal models useful in the study of thrombosis and antithrombotic agents" (1972) Prog. Hemost. Thromb. 1: 165).

[558] However, while animal testing undoubtedly has value, the experts cautioned against automatic extrapolation. In particular, Dr. Sanders and Dr. Rodricks disagreed on the predictability of animal testing to humans regarding toxicity and whether the LD_{50} test was the correct test in these circumstances (Table IV of the '777 Patent).

[559] The evidence adduced before the Court is that, experimentally and scientifically, ticlopidine and PCR 4099 were developed through the use of animal models (particularly the rat). On this issue, the Court refers to Dr. Shebuski's opinion "[w]hen we see a correlation like we see here with ticlopidine and 4099 in these models, and we have a lot of confidence that if we test some new compounds, like the D-enantiomer 25990C, that we will have data that will be very predictive of future human clinical efficacy." (Shebuski, T5053).

[560] As recalled earlier, a line of reasoning is not required to be "certainty" as long as it is "*prima facie*" reasonable.

[561] Thus, the Court agrees with Sanofi that a "track record" reflecting a historical perspective on events had been established. Ticlopidine and PCR 4099 had shown efficacy and safety in the rat model. The animal models used by Sanofi had been used to test two similar compounds, ticlopidine and PCR 4099 prior to 1988. Both of these compounds were active in both the animal models and in humans. Many of the same tests were used for PCR 4099 and clopidogrel. In light of this observed correlation, it was reasonable inference that since clopidogrel was active in the same animal models, it would also be active in humans. It was accordingly reasonable to infer that the "track record" demonstrated that the animal models were predictive and that the correlation was established before 1988. In sum, this was sufficient to conclude that testing in rodents would provide an articulate line of reasoning that could be extrapolated to humans (*Lundbeck Canada Inc. v Canada (Minister of Health*), 2010 FCA 320, 88 CPR (4^{th}) 325). Although the *Lundbeck* case was not a selection case as argued by Apotex, the Court nonetheless is of the opinion that the general principles outlined in *Lundbeck* apply to the case at bar.

(vii) Conclusion on Line of Reasoning

[562] Based on its review of the evidence, the Court finds that Sanofi's understanding of the following elements was central to its sound line of reasoning:

- Stereochemistry: the structure and stereochemical relationship of clopidogrel bisulfate to the previous compounds that had been synthesized and tested by Sanofi, including PCR 4099 and ticlopidine;
- Toxicology: the potential to use pre-clinical toxicity tests to predict clinical toxicity (the toxicological relationship);
- Haematology: ADP is common to all species and was known to be involved in the activation of the platelets;
- Metabolism: clopidogrel as a "pro-drug";
- Previous work on thienopyridine: the track record; and
- Extrapolation: rodents as a good model for extrapolation to humans.

[563] Based on the previously-reviewed evidence which establishes that ticlopidine and PCR 4099 were active in both animals and humans, the Court concludes that Sanofi established a "track record", which in turn provided a sound line of reasoning upon which to predict that clopidogrel had platelet inhibiting activity. This activity was not present in the other enantiomer and clopidogrel was better tolerated and less toxic than the other enantiomer and racemate and, in addition, the L-clopidogrel was not active.

(e) Disclosure

(i) *Quid Pro Quo* – Principles

[564] Justice Hughes in *Eli Lilly Canada Inc. v Apotex Inc.*, 2008 FC 142, 63 CPR (4^{th}) 406, [*Raloxifene*], highlighted the importance of the disclosure requirement for sound prediction:

> [163] The third criterion however is that of disclosure. It is clear that the '356 patent does not disclose the study described in the Hong

> Kong abstract. The patent does not disclose any more than Jordan did. The person skilled in the art was given, by way of disclosure, no more than such person already had. No "hard coinage" had been paid for the claimed monopoly. Thus, for lack of disclosure, there was no sound prediction.
>
> [164] Eli Lilly argues that there is no need for such disclosure. First, it argues that the Hong Kong abstract was already public by the time the Canadian filing was made and that was sufficient disclosure to satisfy the third element of the *AZT* requirements. I disagree. A considered reading of paragraph 70 of the *AZT* decision leads to the conclusion that the disclosure must be in the patent, not elsewhere. The public should not be left to scour the world's publications in the hope of finding something more to supplement or complete a patent disclosure. As the Supreme Court said at paragraph 70, the *quid pro quo* offered in exchange for the monopoly is disclosure. It must be in the patent.
>
> [Emphasis added]

[565] On appeal, the Federal Court of Appeal in *Eli Lilly Canada Inc. v Apotex Inc.*, 2009 FCA 97, 78 CPR (4th) 388: [*Raloxifene* for osteoporosis], provided further guidance on the disclosure requirement:

> [13] The importance of the disclosure obligation in applying for a patent has been emphasized by the Supreme Court of Canada on a number of occasions in recent years (*Pioneer Hi Bred Ltd. v. Canada (Commissioner of Patents)*, [1989] 1 S.C.R. 1623 at paragraph 23; *Cadbury Schweppes Inc. v. FBI Foods Ltd.*, [1999] 1 S.C.R. 142 at paragraph 46; *Free World Trust v. Électro Santé Inc.*2000 SCC 66, [2000] 2 S.C.R. 1024 at paragraph 13; *Apotex Inc. v. Wellcome Foundation Ltd.*,2002 SCC 77, [2002] 4 S.C.R. 153 at paragraph 37 (commonly referred to as *AZT* and hereinafter referred to as such)).
>
> [14] The decision of the Supreme Court in *AZT* is particularly significant to the disposition of this appeal. According to *AZT*, the requirements of sound prediction are three-fold: there must be a factual basis for the prediction; the inventor must have at the date of the patent application an articulable and sound line of reasoning from which the derived result can be inferred from the factual basis; and third, there must be proper disclosure (*AZT*, *supra*, at paragraph 70). As was said in that case (para. 70): "the sound prediction is to some extent the *quid pro quo* the applicant offers in exchange for the patent monopoly". In sound prediction cases there is a heightened

> obligation to disclose the underlying facts and the line of reasoning for inventions that comprise the prediction.
>
> [15] In my respectful view, the Federal Court Judge proceeded on proper principle when he held, relying on *AZT*, that when a patent is based on a sound prediction, the disclosure must include the prediction.
>
> [Emphasis added]

[566] A question arose during the argument phase of the trial regarding whether the discussion by Justice Hughes in [*Raloxifene*] concerning the disclosure requirement for sound prediction had since been overturned by the Federal Court of Appeal or whether it was still sound law.

[567] In the decision of *Novopharm Ltd. v Eli Lilly and Co.*, 2011 FCA 220, 94 CPR (4th) 95, [Novopharm] released after the trial ended, the Federal Court of Appeal confirmed that the disclosure requirement for sound prediction in *Raloxifene* is sound law. Justice Evans stated at paras 46-51:

> (v) *Prediction of utility and the need for disclosure*
>
> [46] After concluding that Teva had established that atomoxetine was not useful because it had not been demonstrated to be an effective treatment for ADHD, the Judge considered whether a POSITA would be able soundly to predict the claimed utility. He held that Lilly could not rely on the principle of sound prediction because it had not disclosed *in the patent* the MGH Study which was the factual basis of the prediction.
>
> [47] Lilly submits that neither the *Patent Act* nor the Supreme Court's jurisprudence requires disclosure of this kind in the patent as a condition precedent to successfully invoking sound prediction as the basis of the utility of the claimed invention. However, while Justice Binnie may not have definitively decided this question in *Apotex Inc. v. Wellcome Foundation Ltd.*, 2002 SCC 77, [2002] 4 S.C.R. 153 at para. 70, it has been held in the Federal Court, and affirmed by this Court, that a patentee must disclose in the patent a study that provides the factual basis of the sound prediction: *Eli Lilly Canada Inc. v. Apotex Inc.*, 2008 FC 142, 63 C.P.R. (4th) 406, *aff'd.* 2009 FCA 97, 78 C.P.R. (4th) 388 (*Eli Lilly Canada*).

> [48] Counsel argued that Lilly had made an international application for the '735 patent. He relied on Article 27(4) of the *Patent Cooperation Treaty*, 1970, 28 U.F.T 7647 (Treaty), which provides that in matters of form or contents required for national patent applications, an applicant can insist that the relevant provision of the Treaty and Regulations be applied to the international application.
>
> [49] In my view, this argument does not assist Lilly. Article 27(5) of the Treaty provides that nothing in the Treaty or the Regulations shall be construed as limiting Contracting States' freedom to prescribe substantive conditions of patentability. Writing for this Court in *Eli Lilly Canada*, Justice Noël stated (at para. 19):
>
> > The appellant further argues that requiring the complete disclosure of the factual basis underlying the sound prediction is inconsistent with the *Patent Cooperation Treaty*… However, this *Treaty* specifically contemplates the supremacy of national law in setting the rules for substantive conditions of patentability (see article 27(5) of the Treaty). We are concerned here with substantive conditions of patentability.
> >
> > [Emphasis in original]
>
> [50] I see no basis in the present case for departing from the normal practice of this Court to follow its own decisions. The decision in *Eli Lilly Canada* was far from being "manifestly wrong" in any of the senses contemplated by *Miller v. Canada (Attorney General)*, 2002 FCA 370, 220 D.L.R. (4th) 149 at para. 10. In view of his ruling on the applicability of Article 27(5), it is immaterial that Justice Noël did not refer in his reasons to Article 27(4).
>
> [51] Indeed, if disclosure in the patent of the factual basis of the prediction of utility was not required for sound prediction, it would be difficult to see what Lilly could be said to have given to the public, in exchange for the grant of the monopoly, that it did not already have. When utility is based on sound prediction, disclosure of its factual foundation goes to the essence of the bargain with the public underlying patentability.
>
> [Emphasis added]

[568] The Court now turns to the disclosure.

(ii) Factual Basis

[569] Sanofi asserts that the factual basis, as disclosed in the ‘777 Patent, is that clopidogrel inhibits platelet aggregation. Sanofi asserts that this fact was established in the pharmacological studies set out in the ‘777 Patent, including:

- A description will now be given of the results of this study which demonstrates another advantage of the invention, … (page 12)
- They demonstrate that the levo-rotatory isomer is inactive and the dextro-rotatory isomer is at least as active as the racemate. (page 13)
- The results shown in Table II demonstrate again that only the dextro-rotatory isomer is active whereas the salts have comparable activities. (page 15)
- The results which are presented in Table III show that the levo-rotatory isomer is inactive in this test, in contrast to the dextro-rotatory isomer and the racemate. (page 17)
- [T]hese results show on the one hand the toxicity of the racemic mixture is similar to that of the levo-rotatory isomer whereas the dextro-rotatory isomer is markedly less toxic, and, on the other hand, that the toxicity depends on the nature of the acid used to form the salt. (page 18)
- The pharmacological study just presented has demonstrated the interesting inhibitory properties towards platelet aggregation of the compound Id and the absence of any activity of its isomer Il. (page 20)

[570] However, the Court is of the opinion that upon reading the ‘777 Patent, it does not instruct the POSITA that there was a factual basis and a line of reasoning for the prediction that the animal studies conducted on rat models could be extrapolated to the prediction that the compound – clopidogrel – had a use in humans. The disclosure in the ‘777 Patent is insufficient.

(iii) Insufficient Disclosure – Essential Elements of Factual Basis Missing

[571] The Court is of the opinion that the ‘777 Patent does not sufficiently disclose the factual basis and sound line of reasoning for the following reasons:

- There is no reference to the work done on ticlopidine;
- There is no reference to the work done on PCR 4099;
- There is no reference to multiple animals used;
- There is no reference to knowledge of convulsions; and
- There is no recognition of the importance of metabolism.

[572] The tests disclosed in the ‘777 Patent are with respect to only one strain of animal, in one gender (female), using only a single time point. There was no disclosure of the factual basis or the line of reasoning for the prediction. There was no basis for the POSITA to make “the leap” to predict use in humans.

[573] The “track record” is crucial in assisting the POSITA to make the leap to predict use of the compound in humans but it is absent from the ‘777 Patent.

1. ***Missing Information***

(a) No Reference to Work done on Ticlopidine

[574] The work on ticlopidine, a component of the “track record” was part of the information and the benefit known to Sanofi’s scientists. This work would later inform the work on PCR 4099 which in turn would eventually lead to work on clopidogrel. The ticlopidine results – or example that the dextro-levatory enantiomer was thirty (30) times more potent than ticlopidine – are not found in the ‘777 Patent. There is simply no mention of ticlopidine in the ‘777 Patent. Reliance upon the results of ticlopidine in terms of activity is thus not found in the '777 Patent (Shebuski, cross T5278-5282).

(b) No Reference to PCR 4099

[575] PCR 4099 was a novel antiaggregating agent derived from ticlopidine.

[576] The Court notes that, while it is true that PCR 4099 was published in various abstracts (discussed later in the Anticipation and Obviousness sections of this decision), its properties were not part of the general common knowledge. The circumstances are similar to those in the case in *Eli Lilly Canada Inc. v Apotex Inc*., 2008 FC 142, [2008] FCJ No 171, where studies known as the "Hong Kong studies" were absent from the patent. Justice Hughes stated that "the public should not be left to scour the world's publications". The same holds true in the present case as far as PCR 4099 is concerned.

[577] Specifically, a number of pertinent informative elements relating to PCR 4099, which would allow the POSITA to understand the progression from ticlopidine to PCR 4099 and clopidogrel, are absent from the '777 Patent. For instance:

- PCR 4099 is totally inactive *in vitro* and platelet aggregation and is practically inactive after IV administration.
- The antiaggregating effect of the PCR 4099 is associated with platelets.
- PCR 4099 is highly potent in rats against the main agonist.
- The antiaggregating effects in baboons.
- The three models of thrombosis used on PCR 4099: i) the arterial venous shunt model, ii) the metallic coil model, and iii) the stasis induced thrombosis model.
- The activity of PCR 4099 could be mediated by metabolite but at this time no such active metabolite has been identified.
- The acute toxicity of PCR 4099 was evaluated in two rodent species, rat and mouse.
- A sex difference was found in rodents administered with the test compound orally.
- Long-term studies of toxicity were carried out in rats and baboons by the oral route.

(Hirsh, Re-Exam T721-728)

(c) No Reference to Multiple Animal Models used and Knowledge of Convulsions

[578] In addition to the above, the Court observes that the POSITA would not know that PCR 4099 was tested on baboons and rabbits. But more importantly, the POSITA would have no way of knowing that convulsions in baboons were allegedly key to the decision to cease the work on PCR 4099 and to pursue the splitting of the enantiomers. That knowledge was private. It was not public. The POSITA would have no reason to know that there is a differential toxicity issue with PCR 4099. Indeed, even the abstracts on PCR 4099 indicate that there is no problem with the racemate. Thus, the POSITA would not be able to deduce that, knowing that the L-enantiomer was toxic, the toxicity seen in the one-year baboon study was most likely due to the L-enantiomer which comprises 50% of PCR 4099.

[579] On this point, the Court recalls that the "Simon Memo" dated April 16, 1987, sent by Mr. Pierre Simon, Director of Research and Development at Sanofi Research, states that the studies conducted on PCR 4099 will cease allegedly due to convulsions. This begs the question: if the issue of the convulsions was so important as to halt the studies on PCR 4099 so late in the day and following a considerable investment by Sanofi, would it not be important for the reader to know that there was a significant toxicity risk with PCR 4099? This information is not in the '777 Patent.

(d) No Recognition of Importance of Metabolism

[580] The POSITA reading the '777 Patent would know that clopidogrel is a pro-drug and would therefore understand the importance of metabolism and the "unbreachable firewall" discussed by Dr. Levy. Likewise, Dr. Maffrand understood the vital role played by metabolite and testified to its

importance. Yet, nowhere in the ‘777 Patent is there a discussion on metabolite. This discussion is key in order to disclose this hurdle and allow the POSITA to make the leap.

2. ***Disclosure: A Reference in the ‘777 Patent***

[581] During final argument, Sanofi submitted that there was a reference to ticlopidine and PCR 4099 in the ‘777 Patent. More specifically, Sanofi alleged that the ‘777 Patent refers to the Kumada paper and that ticlopidine is one of the compounds studied in that paper. Therefore, for Sanofi, the reference to the Kumada test means that this was a test that was measured on ticlopidine. In addition, Sanofi argues that the ‘777 Patent made reference to PCR 4099. Sanofi further relied on page 1 of the ‘777 Patent and argued that it refers to the French racemate patent, i.e. the French application 2530247.

[582] The Court cannot agree with Sanofi’s contentions in this regard. Sanofi’s argument stretches the reference to ticlopidine in the ‘777 Patent which implies a weakened duty of disclosure. If an element is essential, as the Court deems the progression from ticlopidine, to PCR 4099 and finally to the ‘777 Patent to be, it should be <u>in</u> the patent itself and not a couple of steps removed in a reference to another document (*Eli Lilly Canada Inc. v Apotex Inc.*, 2008 FC 142, [2008] FCJ No 171; *Eli Lilly Canada Inc. v Apotex Inc.*, 2009 FCA 97, [2009] FCJ No 404). This issue was recently considered by the Federal Court of Appeal in *Apotex Inc. v Pfizer Canada Inc.*, 2011 FCA 236, [2011] FCJ No 1234, at paras 43-44, where the importance of the bargain of patent law inherent in the disclosure requirement was underscored as follows:

> [43] At the hearing, counsel for Pfizer argued that the line of reasoning was to be found in the studies listed in the “References” section of the patent (Patent ‘132, at pages 30 and 31). Pfizer also took the position that a POSITA, taking the prior art as a whole, would be able to infer that

> multiple doses of latanoprost would give the same results as the single dose studies.
>
> [44] This position seems at odds with the concept of disclosure in patent law. In *Wellcome AZT*, Justice Binnie stated that if utility is not demonstrated at the time of filing, the *quid pro quo* the applicant offers in exchange for the patent monopoly is a sound prediction of utility (*Welcome AZT*, at paragraph 70). As the applicant is the one who will benefit from the monopoly, I am of the view that only he, and not the authors or inventors of the prior art, can discharge himself of the obligation of disclosure. Besides, our Court found in *Eli Lilly Canada Inc. v. Apotex Inc.*, 2009 FCA 97, at paragraph 17 that a patent that provides no more disclosure than is available in the prior art does not provide a sound basis for the prediction.

[583] Thus, the Court cannot consider any disclosure that, specifically a reference to the patent, does not meet the "*quid pro quo*" inherent to disclosure requirement imposed by patent law.

(4) Conclusion on Disclosure

[584] In conclusion, on the question of disclosure, the Court finds that there is insufficient disclosure in the '777 Patent because it does not disclose the underlying facts (e.g. work on thienopyridines and PCR 4099) nor a sound line of reasoning (e.g. ticlopidine, PCR 4099, convulsions, metabolism). Thus the underlying factual basis and line of reasoning that grounded the inventor's alleged prediction were not disclosed.

F. *Conclusion on Sound Prediction*

[585] Apotex has persuaded the Court that, on balance of probabilities, the disclosure in the '777 Patent was insufficient. For that reason, claims in the '777 Patent are found to be invalid for lack of sound prediction. Indeed, "…it would be difficult to see what [Sanofi] could be said to have given to the public, in exchange for the grant of the monopoly, that it did not already have…" (*Novopharm*, para 51).

[586] Given this conclusion, there is no need to address other grounds of invalidity but the Court will nonetheless advance its views on the balance of the arguments advanced by Apotex. Hopefully, they will be of assistance.

VIII Obviousness

A. *General Principles*

[587] Sanofi's overall position on obviousness can be summarized as follows: it is admitted by witnesses for both parties that a POSITA would have been unable to predict the properties of clopidogrel until the racemate, PCR 4099, had first been separated and its individual enantiomers, one of which is clopidogrel, tested. Further, clopidogrel has clear unexpected advantages over the other members of the genus, which clearly support the patentability of this selection invention.

[588] As for Apotex, it maintains that the invention in the '777 Patent was obvious.

[589] In *Plavix*, the Supreme Court of Canada provided a four-step approach for assessing obviousness at paras 67 to 69:

> [67] …
>
> (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 in original]

It will be at the fourth step of the *Windsurfing/Pozzoli* approach to obviousness that the issue of "obvious to try" will arise.

> i. When Is the "Obvious to Try" Test Appropriate?
>
> [68] In areas of endeavour where advances are often won by experimentation, an "obvious to try" test might be appropriate. In such areas, there may be numerous interrelated variables with which to experiment. For example, some inventions in the pharmaceutical industry might warrant an "obvious to try" test since there may be many chemically similar structures that can elicit different biological responses and offer the potential for significant therapeutic advances.
>
> ii. "Obvious to Try" Considerations
>
> [69] If an "obvious to try" test is warranted, the following factors should be taken into consideration at the fourth step of the obviousness inquiry. As with anticipation, this list is not exhaustive. The factors will apply in accordance with the evidence in each case.
>
> (1) Is it more or less self-evident that what is being tried ought to work? Are there a finite number of identified predictable solutions known to persons skilled in the art?
>
> (2) What is the extent, nature and amount of effort required to achieve the invention? Are routine trials carried out or is the experimentation prolonged and arduous, such that the trials would not be considered routine?
>
> (3) Is there a motive provided in the prior art to find the solution the patent addresses?

[590] The Supreme Court of Canada also provided the following additional guidance in assessing obviousness, at paras 70-71:

> [70] Another important factor may arise from considering the actual course of conduct which culminated in the making of the invention. It is true that obviousness is largely concerned with how a skilled worker would have acted in the light of the prior art. But this is no reason to exclude evidence of the history of the invention, particularly where the knowledge of those involved in finding the invention is no lower than what would be expected of the skilled person.

> [71] For example, if the inventor and his or her team reached the invention quickly, easily, directly and relatively inexpensively, in light of the prior art and common general knowledge, that may be evidence supporting a finding of obviousness, unless the level at which they worked and their knowledge base was above what should be attributed to the skilled person. Their course of conduct would suggest that a skilled person, using his/her common general knowledge and the prior art, would have acted similarly and come up with the same result. On the other hand, if time, money and effort was expended in research looking for the result the invention ultimately provided before the inventor turned or was instructed to turn to search for the invention, including what turned out to be fruitless "wild goose chases", that evidence may support a finding of non-obviousness. It would suggest that the skilled person, using his/her common general knowledge and the prior art, would have done no better. Indeed, where those involved including the inventor and his or her team were highly skilled in the particular technology involved, the evidence may suggest that the skilled person would have done a lot worse and would not likely have managed to find the invention. It would not have been obvious to him/her to try the course that led to the invention.

B. *Date of Invention*

[591] The Court observes that in assessing obviousness under the Old Act, the relevant date is the date of the invention (*Xerox of Canada Ltd. et al v IBM Canada Ltd.* (1977), 33 CPR (2^{nd}) 24 (FCTD); SCC *Plavix* decision at para 52). It is for the Court to determine the date of the invention.

[592] As discussed in Section I there is only one invention in the '777 Patent and the invention relates to the salts and its advantages. The Court recalls that there is no issue between Apotex and Sanofi concerning the inventive concept of the '777 Patent.

[593] The Court further recalls that the inventive concept of the '777 Patent was described by the Supreme Court of Canada in *Plavix* at para 78 as follows:

> [78] In the present case, it is apparent that the inventive concept of the claims in the '777 patent is a compound useful in inhibiting platelet aggregation which has greater therapeutic effect and less

> toxicity than the other compounds of the ‘875 patent and the methods for obtaining that compound.

[594] However, the parties are in disagreement as to the date of the invention.

[595] Sanofi asserts two possible invention dates. The first one is April 1986 and corresponds to the date that Mr. Badorc first successfully resolved PCR 4099. The second date of invention alleged by Sanofi is December 1986 which is the date Dr. Fréhel prepared a handwritten first draft of the priority application for the ‘777 Patent.

[596] Apotex, on the other hand, maintains that the date of the invention is between May 1987 and November 1987 as the properties of the salts were ascertained during this timeframe.

[597] Upon considering the evidence, the Court cannot agree with either date advanced by Sanofi because neither the date of April 1986 nor the date of December 1986 makes reference to the salts which were an integral part of the invention in the ‘777 Patent. While it is true that the date of April 1986 corresponds to the date when PCR 4099 was first resolved, the properties of the salts at that date had yet to be ascertained. As for the date of December 1986, it finds support in a handwritten document which refers to tolerability. In that document, Dr. Fréhel writes that it has unexpectedly been discovered that the dextro-rotatory enantiomer has the activity for inhibition of platelet activity and that the levo-rotatory enantiomer is inactive. Also, the levo-rotatory enantiomer, the inactive enantiomer, is less well tolerated of the two enantiomers. However, again, the document does not refer to salts.

[598] The Court notes that the relevant date for the invention is the date when the inventor can prove he has first formulated the invention. This principle was enunciated in *Rice v Christiani & Nielson*, [1930] SCR 443, in Justice Rinfret's interpretation of the judgment of the *Privy Council in Canadian General Electric Co. v Fada Radio Ltd*., [1930] AC 97, 47 RPC 69, [1930] 1 DLR 449:

> ... by the date of discovery of the invention is meant the date at which the inventor can prove he has first formulated, either in writing or verbally, a description which affords the means of making that which is invented. There is no necessity of a disclosure to the public. If the inventor wishes to get a patent, he will have to give the consideration to the public; but, if he does not and if he makes no application for the patent, while he will run the risk of enjoying no monopoly, he will none the less, if he has communicated his invention to "others", be the first and true inventor in the eyes of the Canadian patent law as it now stands, so as to prevent any other person from securing a Canadian patent for the same invention.
>
> [Emphasis added]

[599] As such, without the salts, the invention cannot be said to have been reduced to a definite and practical shape. Thus, neither the date of April 1986 nor the date of December 1986 can be the date of the invention. The evidence demonstrates that the properties of the salts were ascertained between May 1987 and November 1987. After considering the evidence, the Court accordingly agrees with Apotex that the invention date must be November 6, 1987.

[600] Thus, the Court will address the question of obviousness as of the date of the invention, November 6, 1987.

C. *Common General Knowledge*

[601] The Court must now determine the common general knowledge as of November 6, 1987.

[602] At issue in this case for assessing the common general knowledge are the following:

1. The state of the art of science in 1987
2. The ‘875 Patent
3. The abstracts and posters at the 1985 and 1986 conferences
4. The 1987 FDA Policy
5. The Ariens Article
6. PCR 4099

[603] Is the prior art admissible for common general knowledge? In order to be admissible, the prior art must have been publicly available as of the date of invention – *i.e.* November 6, 1987 – and it must further be locatable through a reasonably diligent search. The burden is on the party relying upon the prior art to establish that it could be found in a reasonably diligent search (*Janssen-Ortho Inc. v Novopharm Ltd*., 2006 FC 1234, 57 CPR (4th) 6), in this case, Apotex.

[604] The Court also notes that common general knowledge means the knowledge known by the person of ordinary skill in the art (*Eli Lilly & Co. v Apotex Inc*., above, at paras 95-100).

(1) The State of the Art of Science

[605] In 1987, the evidence demonstrated that there was a clinical need for a better antiplatelet drug. The only such drugs that were available in 1987 were Aspirin and dipyridamole. At that time, Sanofi had disclosed ticlopidine, which is part of the thienopyridine compound family.

[606] In its opening statement, Apotex provided helpful suggestions as to what constituted the state of the art of science. In the Court’s view, there are a number of areas mentioned by Apotex that should be considered as state of the art of science.

[607] In general terms, the state of the art includes the following concepts:

- the haemostatic system (including platelet function);
- the principles of stereochemistry;
- the pharmacology and pharmacokinetics of chiral drugs;
- the pre-clinical pharmacological and toxicological testing and its limitations;
- the methods of preparing homochiral compounds;
- the preparation of useful acid addition salts in pre-formulation studies; and
- the formulation of compounds for human administration.

(2) The ‘875 Patent

[608] Sanofi concedes that the ‘875 Patent was in the common general knowledge of the skilled person. Dr. Byrn testified in that respect.

[609] However, Sanofi argues that the ‘875 Patent does not specifically disclose or teach (i) the hydrogen sulfate salt of clopidogrel, nor how to obtain the dextro-rotatory enantiomer, nor their unique and valuable combination of properties or, that (ii) there are any benefits associated with a particular enantiomer or a salt of a particular form.

[610] In this regard, Apotex argues that the ‘875 Patent asserted that its compounds, including PCR 4099 and each of its two enantiomers and their pharmaceutically-acceptable salts (including the bisulfate salt), were useful antiaggregants/antithrombotics with excellent tolerance and low toxicity, making them very useful for human therapeutic applications.

[611] It is important to recall that the ‘875 Patent relates to a vast genus consisting of approximately 9.5 million different compounds. In particular, the Court notes that the ‘875 Patent featured PCR 4099 as the lead compound. Of the many compounds mentioned in the patent, only

twenty-one (21) are exemplified. The very first, Derivative 1, is PCR 4099. The results of four (4) pharmacological tests on seventeen (17) of the exemplified compounds are given in the ‘875 Patent. PCR 4099 and Derivative 10 are the only compounds tested in each experiment. Further, PCR 4099 is the most potent compound in each test, showing stronger activity at doses lower than the doses at which the other compounds were tested. Assuming that a chemist chose example 1 of the ‘875 Patent and decided to separate it on the basis that Claim 1 of the ‘875 Patent states “are separated if desired”, the evidence adduced by Dr. Byrn and Dr. Davies is to the effect that it would have been difficult to separate PCR 4099 without undue burden. The ‘875 Patent did not teach the skilled reader how to separate or what the advantages of the separation would be.

[612] After reading the ‘875 Patent and considering the evidence, the Court is of the opinion that the ‘875 Patent does not, either directly or indirectly, point to PCR 4099 or to clopidogrel.

[613] Although it is undisputed that PCR 4099 and clopidogrel are encompassed within the ‘875 Patent, clopidogrel and its bisulfate salts are not specifically disclosed or claimed in the ‘875 Patent. Indeed, the ‘875 Patent does not (i) teach the method to separate or isolate the enantiomer; (ii) provide examples on how to prepare enantiomers or, (iii) teach that clopidogrel will be less toxic, better tolerated and have better activity.

[614] However, the Court is of the opinion that the compound PCR 4099 (not its properties), Derivative 1 of the ‘875 Patent, would form part of the common general knowledge that a person of ordinary skill in the art could find by undertaking a reasonably diligent search of patent applications.

(3) The Abstracts and Posters at the July 1985 Conference in San Diego and the June 1986 Conference in Jerusalem

[615] Two of Sanofi's abstracts and posters were the subject of much debate at trial. They are the July 1985 San Diego Conference abstract and the June 1986 Jerusalem Conference abstract.

[616] Sanofi's scientists made presentations at both of these conferences in San Diego and Jerusalem and identified PCR 4099 as its lead compound. The abstracts with respect to the Xth International Congress on Thrombosis and Haemostasis held in San Diego were published in Thrombosis and Haemostasis in 1985. The abstracts with respect to the Joint meeting of the International Committee on Thrombosis and Haemostasis; 32nd annual meeting and the Mediterranean League against Thromboembolic Diseases; 9th Congress held in Jerusalem were published in Thrombosis Research in 1986.

[617] The Court observes that in order to be relevant to the issue of obviousness, the posters and the abstracts must consist of something which, on the evidence, was either available to a person of ordinary skill in the art or that they could reasonably be assumed to have had knowledge of in 1987 (*Mahurkar v Vas-Cath of Canada Ltd*. (1988), 18 CPR (3d) 417 (Fed TD), at 432-36, aff'd (1990), 32 CPR (3d) 409 (Fed CA)).

[618] Dr. Hirsh explained that, generally speaking, scientists send an abstract in advance of a conference. They consist of documents limited in length and size which are then reviewed and rated by a scientific committee for the conference at issue. The abstracts that are rated above a certain minimal level are accepted either for presentation or for poster presentation.

[619] Dr. Colman explained that a participant at a conference, akin to the San Diego and Jerusalem conferences in the mid-1980's, would have received the abstract book before the conference meeting. The abstracts are published in a book, and the book is typically sent ahead of time to the conference delegates and can be purchased at the conference. The book of abstracts would contain an important number of abstracts. At the conference, participants interested in learning more about a particular abstract could attend a poster presentation.

[620] During these conferences, conference rooms were set aside for poster presentations. The poster would be displayed in a conference room for a couple of days, usually pinned with thumbtacks on the wall. The poster would contain the entire presentation with all the data included and the person designated as being responsible for discussing the poster would be there for a shorter period of time (Hirsh, T555). Posters could be given out at the meeting. Dr. Colman and Dr. Hirsh testified that unless the posters were given out to the participants at the poster presentation, the participants would not have received a copy. The posters were not part of the abstract book.

[621] Against this background, the Court recalls that Apotex argues that the abstracts were published in leading journals and regularly reviewed by persons in the field. Sanofi, however, is of the view that the abstracts were not available to a POSITA.

[622] After considering the evidence, the Court agrees with Sanofi and finds that Apotex has failed to provide evidence establishing that either the abstracts or the posters could be located by way of a reasonably diligent search.

[623] Regarding the abstracts in particular, the evidence and notably Dr. Colman's testimony were not conclusive on the issue of whether they could be located in a search or using key words from journal indexes at the relevant time.

[624] Importantly, the Court recalls that, in the mid-1980's, research was conducted in libraries. There was no internet providing information in an instantaneous and electronic fashion. The evidence submitted on this point by Apotex based on a recent PubMed search in 2011, while interesting, failed to persuade the Court in this regard.

[625] Indeed, the PubMed internet service search tool presented at trial was simply not available at the relevant date. At most, Apotex merely established that the journals could be located using the internet in 2011. Further, Apotex' visual presentation at trial demonstrating that the abstracts are currently indexed online by keyword in Science Citation Index (a paper version of Science Citation Index was a tool used by skilled researchers and librarians in the 1980's) does in no way convince the Court that a reasonable and diligent search would have allowed the abstracts to be located at the relevant date. On the basis of the evidence, the Court does not agree with Apotex' experts who opined that the abstracts would be known by the skilled person or would have been readily located by the person of ordinary skill in the art interested in the state of the art of antiplatelet agents.

[626] Regarding the posters, the evidence adduced by Sanofi clearly establishes that they were not published and would not have been available or possibly located by way of a reasonable and diligent search. The mere fact that posters on PCR 4099 were displayed at the San Diego and Jerusalem conferences is insufficient to convince the Court that they became part of the common

general knowledge. Indeed as stated by the Court in *Janssen-Ortho Inc. v Novopharm Ltd*., at para 57:

> [57] …[A] public display for three hours at a scientific meeting does not mean that the poster has entered into the body of prior art of which a person skilled in the art could be said to possess or of which they could make themselves aware through a reasonably diligent search.

[627] In addition, although Dr. Colman and Dr. Hirsh testified that thousands of participants, academics, pharmaceutical companies with a particular interest in antiplatelet drugs, students and clinical practitioners interested in clinical research would attend the conferences of San Diego and Jerusalem, the fact of the matter is that a much smaller number of participants would have been interested in attending the poster presentation and discussing it with Sanofi's designated individual. Sanofi was not the only pharmaceutical company providing a poster presentation at these conferences. There were many other poster presentations to attend in many other conference rooms. Although the posters might have been distributed in small numbers, the evidence further demonstrates that they did not form part of the book of abstracts and were not published.

[628] Therefore, the Court finds that the abstracts and the posters from the July 1985 San Diego Conference and the June 1986 Jerusalem Conference do not form part of a body of prior art that was known to or could in any reasonable way have been found by a person of ordinary skill in the art as of 1987.

(4) The 1987 FDA Manufacturing Guidelines

[629] Another document was the source of much debate: the 1987 Food and Drug Administration in the United States Manufacturing Guidelines (1987 FDA guidelines).

[630] The 1987 FDA guidelines stated that racemic new drugs should ideally be separated and studied prior to being submitted for approval, and that physical/chemical information should be provided or may be requested. Pursuant to the 1987 FDA guidelines, the official FDA policy on the issue of stereoisomers would be introduced some years later in 1992 – which is after the relevant date. The issue is the following: Can the 1987 FDA guidelines be considered part of the common general knowledge as of the date of the invention, *i.e.* November 1987?

[631] Sanofi's position with respect to the 1987 FDA guidelines is that no witness identified this document, whereas Apotex argues that in February 1987, the FDA circulated the guidelines.

[632] As far as the Court is concerned, the origin of the document and the extent of its circulation remains a mystery. Neither the testimonies of witnesses nor any related evidence clarified this mystery. Indeed, Dr. Wainer testified that he was given the document by counsel for Apotex (Wainer, cross T1328). He did not know where the document came from and agreed that it did not come from any publication. Dr. Wainer, who worked at the FDA but had left the organization by 1987, confirmed that he was not on the stereoisomer committee which developed the 1992 policy.

[633] Dr. Weissinger, for her part, who chaired the FDA stereoisomer committee, wrote the 1992 Policy and was positioned higher in the hierarchy organization of the FDA than Dr. Wainer. Dr. Weissinger testified that she only saw the 1987 FDA guidelines in 1989 after the stereoisomer committee was formed. She also testified that she had discussions about the guidelines when she was sitting on the FDA stereoisomer committee with one of her colleagues, Mr. De Camp.

[634] The Court further recalls that, in cross-examination, Dr. Davies was provided by counsel for Apotex with a copy of Dr. Davies' transcript from the U.S. proceeding (D-190). In that transcript, there was a document that was characterized as the 1987 FDA guidelines. This created the impression that the 1987 FDA guidelines could have been in circulation at that date. However, the evidence establishes that the document Dr. Davies saw in the U.S. proceeding was a different document containing a different pagination than the 1987 FDA guidelines. This document states the following:

> Note: This Guideline was prepared by Dr. Arthur Shaw, Food and Drug Administration, for a Course offered by the Center for Professional Advancement in March of 1994. There have been no changes in the text from the printed version of the Guideline. However, the text has been reformatted to reduce the number of pages. The Table of Contents reflects the new pagination. The old pagination is noted in the Guideline. (D-190)

[635] Hence, the document is dated March 1994 and was thus not available prior to that date.

[636] The Court finds that the evidence relating to the circulation and availability of the 1987 FDA guidelines remains unconvincing. There is considerable uncertainty concerning the circulation of the 1987 FDA guidelines and whether they were published and, in the affirmative, when they were published. At best, the 1987 FDA guidelines were an internal document to the FDA prior to becoming policy in 1992. Upon the creation of the FDA stereoisomer committee in 1989, the committee started its work and the 1987 FDA guidelines logically became a starting point. Three (3) years later, the 1987 FDA guidelines morphed into the 1992 FDA policy.

[637] It should also be noted that the 1987 FDA guidelines were also referred to in the case of *Novo Nordisk Canada Inc. v Cobalt Pharmaceuticals Inc.*, 2010 FC 746, 86 CPR (4th) 161. However, the evidence before Justice Mactavish is in stark contrast from the evidence adduced in the case at bar. Furthermore, the date of the invention in *Novo* was June 21, 1991, which is in a different period (in fact a different decade) from the case at bar. Given these differences, parallels with the *Novo* case are difficult to draw.

[638] Consequently, on the basis of the evidence, the Court concludes that the document entitled the 1987 FDA guidelines could not have been located in a reasonably diligent search and cannot be considered part of the common general knowledge in November 1987. However, this does not mean that there were no discussions regarding the paradigm shift on how to approach racemic drugs. This will be discussed later in the decision.

(5) The Ariens Article

[639] The Ariens article published in 1984 was referred to on a number of occasions during trial and many experts testified to having knowledge of this article.

[640] Dr. Ariens was thought-provoking and expressed the view that due to the different pharmacological and toxicological effects associated with the different enantiomers of a molecule, it was an exercise in “sophisticated nonsense” to ignore the stereochemistry of a given compound. Dr. Wainer provided a good and helpful summary of Dr. Ariens’ approach.

[641] Dr. Ariens was a toxicologist and a pharmacologist who worked in Europe. He began to publish that there could be expectation that enantiomers would differ. Dr. Ariens began to do this to quantify, codify and examine these differences.

[642] In particular, Dr. Ariens published a paper entitled “Stereochemistry, a Basis for Sophisticated Nonsense in Pharmacokinetics and Clinical Pharmacology”, European Journal of Pharmacology (1984) 26: 663-668). In this paper, Dr. Ariens takes a look at how a drug is absorbed, metabolized and excreted. Dr. Ariens’ view was that stereochemistry provides the full picture and had to be taken into consideration. He posited that the body is chiral and the work has to be performed in a chiral environment.

[643] Dr. Ariens proposed the eudismic ratio. In taking two hands of the molecule (the enantiomers), one will be active. The active molecule will be measured and tested in the body. If the molecule is the selected one, it will be called eutomer. This study will be repeated with another molecule to see whether it is toxic or whether it works in the body. Upon completion of the study, a ratio will be established. The usefulness of the drug will then be decided based on a measurement of the positive aspects and the negative aspects. This eudismic ratio could then be used to direct how drugs are developed.

[644] The Court also finds that the Ariens article would have been located in a reasonably diligent search, and thus formed part of the common general knowledge in November 1987.

(6) PCR 4099

[645] In terms of assessing common general knowledge in 1987, a further question is whether the properties of PCR 4099 were generally known. Apotex has not convinced the Court on this point. There are in fact two (2) aspects to this question: (1) did PCR 4099 form part of the common general knowledge and (2) would the properties of PCR 4099 have been found in a reasonably diligent search? Of all of Apotex' experts, Dr. Hirsh was undoubtedly the one in the best position to be aware of the development of novel antithrombotic compounds during the mid-1980's, as he was working in the field at the time. He testified that he was not aware of PCR 4099 until much after 1987. Another of Apotex' experts, Dr. Adger, testified that the earliest he became aware of PCR 4099 was in 1990. The properties of PCR 4099 would not have form part of the common general knowledge. This does not, however, mean that the compound PCR 4099 did not form part of the common general knowledge.

[646] The Court observes that, assuming that the posters and abstracts had formed part of the common general knowledge, which the Court has ruled out, these posters and abstracts made reference to the great potential of PCR 4099 and promised a racemic drug with good activity and low toxicity. This wording, more particularly in the abstracts, provided no indication of a problem with PCR 4099 and therefore no reason, incentive or motivation leading to a separation of PCR 4099.

[647] Thus, the Court concludes that while PCR 4099 did form part of the common general knowledge, its properties would not have been found in a reasonably diligent search.

D. *Test of Obviousness*

[648] The Court now turns to applying the four-stage analysis test described by the Supreme Court of Canada in the *Plavix* decision.

(1) Identify the Notional "Persons Skilled in the Art"

[649] The qualifications of the POSITA (persons of ordinary skill in the art) are set above in paras 64-80. The POSITA is a group of individuals, as opposed to one individual, holding a Ph.D. in pharmaceutical chemistry, with several years of experience working in the fields of pharmacology and toxicology, with good general knowledge of haematology and medicine.

(2) Identify the Relevant Common General Knowledge of that Person

[650] Sanofi argues that the parties are in substantial agreement with respect to the relevant common general knowledge of the POSITA in 1986/1987. This relevant common knowledge would include an understanding of the following:

- the underlying principles of chemistry including chirality, enantiomers, stereoisomers, racemates and optical activity; and
- the knowledge and experience with the general methods of resolving racemates.

[651] However, the parties are not in agreement on two (2) areas that Apotex asserts would form part of the common general knowledge of a POSITA. These areas are (i) the alleged 1987 FDA guidelines, and (ii) the awareness of the properties of PCR 4099 as a potential antithrombotic agent based upon the abstracts and posters.

[652] The Court has already summarized what was part and what was not part of the common general knowledge as follows:

> - the knowledge of haemotology / pharmacology / toxicology, chirality, enantiomers, stereoisomers, racemates and optical activity; and knowledge and experience with the general methods of resolving racemates;
> - the knowledge of the '875 Patent (but the '875 Patent does not disclose clopidogrel);
> - the abstracts and posters presented at the San Diego and Jerusalem conferences were not well known and did not form part of the common general knowledge;
> - the 1987 FDA guidelines did not form part of the common general knowledge; and
> - the properties of PCR 4099 were not part of the common general knowledge although the compound of PCR 4099 formed part of the common general knowledge.

(3) Identify the Inventive Concept of the Claim in Question or if that Cannot Readily be Done, Construe It

[653] The Supreme Court of Canada in *Plavix*, at para 78, identified the inventive concept and there is no reason to depart from this concept:

> [78] In the present case, it is apparent that the inventive concept of the claims in the '777 Patent is a compound useful in inhibiting platelet aggregation which has greater therapeutic effect and less toxicity than the other compounds of the '875 Patent and the methods for obtaining that compound.

(4) 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

[654] The evidence adduced in the case at bar demonstrates that none of the prior art describes clopidogrel, the bisulfate salt of clopidogrel, a process to make clopidogrel or its bisulfate salts, or the beneficial properties of clopidogrel and its bisulfate salt.

[655] The evidence is therefore consistent with the Supreme Court of Canada's finding in *Plavix* at paras 79-80:

> [79] The '875 patent disclosed over 250,000 possible different compounds predicted to inhibit platelet aggregation. Twenty-one compounds were made and tested. Nothing distinguishes the racemate in this case from other compounds disclosed or tested in terms of therapeutic effect or toxicity. As stated above, there is no disclosure in the '875 patent of the specific beneficial properties associated with the dextro-rotatory isomer of this racemate in isolation; nor was there disclosure of any advantages which flow from using the bisulfate salt of the dextro-rotatory isomer. The '875 patent did not differentiate between the properties of the racemate, its dextro-rotatory isomer and levo-rotatory isomer or indeed the other compounds made and tested or predicted to work.
>
> [80] On the other hand, the '777 patent claims that the invention of the dextro-rotatory isomer of the racemate, clopidogrel, and its bisulfate salt discloses their beneficial properties over the levo-rotatory isomer and the racemate and expressly describes how to separate the racemate into its isomers.

[656] It is thus clear that there is more identified in the '777 Patent than what was in the common general knowledge.

(5) 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?

[657] The Court recalls that it is at this step of obviousness approach that the issue of "obvious to try" arises.

E. *"Obvious to Try" Considerations*

[658] In addressing "Obvious to Try" considerations, it is worth noting from the outset that "obvious to try" does not mean "worth a try". The Court agrees with Sanofi that the Supreme Court

of Canada used the "obvious to try" test, such that it is self-evident that it ought to work. This test represents a different and higher standard than the "worth a try" test.

[659] In *Pfizer Canada Inc. v Apotex Inc.*, 2009 FCA 8, 72 CPR (4th) 141, at paras 45-46, the Federal Court of Appeal discussed the issue of "obvious to try" and "worth a try" and clearly rejected the latter:

> [45] In contrast, the test applied by Mr. Justice Laddie appears to be met if the prior art indicates that something may work, and the motivation is such as to make this avenue "worthwhile" to pursue (*Pfizer Ltd.*, *supra*, para. 107, as quoted at para. 42 above). As such, a solution may be "worthwhile" to pursue even though it is not "obvious to try" or in the words of Rothstein J. even though it is not "more or less self-evident" (*Sanofi-Synthelabo*, *supra*, para. 66). In my view, this approach which is based on the possibility that something might work, was expressly rejected by the Supreme Court in *Sanofi-Synthelabo*, at paragraph 66.
>
> [46] The Federal Court Judge rendered his decision on the basis that more than possibilities were required. He concluded based on the evidence before him that Apotex had failed to establish more than that. In so doing, he applied the correct test.

[660] The legal test is thus "obvious to try".

[661] In *Plavix*, the "obvious to try" test was warranted and the Court will look at the following factors:

- Is it more or less self-evident that what is being tried ought to work? Are there a finite number of identified predictable solutions known to persons of ordinary skill in the art?
- What is the extent, nature and amount of effort required to achieve the invention? Are routine trials carried out or is the experimentation prolonged and arduous, such that the trials would not be considered routine?
- Is there a motive provided in the prior art to find the solution the patent addresses?

- What was the actual course of conduct that culminated in the invention?

[662] The Court will now address each of these four questions in turn.

(1) Is it more or less self-evident that what is being tried ought to work? Are there a finite number of identified predictable solutions known to Persons of Ordinary Skill in the Art?

[663] The question of "whether it was more or less self-evident that what is being tried ought to work" is relevant to the issue of (a) the methods available to separate the enantiomers of PCR 4099 and (b) the methods available to obtain the salts. The Court must determine whether it would have been self-evident to a person of ordinary skill in the art that choosing a method to separate and a method to obtain the salts ought to work.

(a) Methods to Separate

[664] In order to determine whether what was being tried was obvious – *i.e.* resolving the racemic compound ought to work – the Court must first look at the methods known to separate enantiomers and which ones were available in 1987.

[665] The evidence demonstrates that there were only four (4) methods available to the POSITA in 1987:

- mechanical separation of crystals;
- Pasteur method (resolution by formation of diastereomers);
- preparation of pure enantiomers by asymmetric synthesis or asymmetric transformation;
- chiral HPLC.

[666] Out of these four (4) methods, two (2) relevant ones were the subject of debate at trial: the Pasteur method and the chiral HPLC method.

(i) What is the "Pasteur Method"?

[667] The Pasteur method, also called the diastereomeric salt resolution method, or the "classic" method, was developed by the French scientist Louis Pasteur in the 1850s. This method is used for resolving racemic compounds in forming and fractionally crystallizing diastereomers. Dr. Adger and Dr. Davies opined that it is a method found in leading textbooks, taught to undergraduate chemists, and widely practiced for over 100 years. Mr. Badorc informed the Court that he had been taught this method during his two (2) year degree in France.

[668] Apotex argues that the skilled person would understand that PCR 4099 was a compound having features that made it particularly amenable to resolution by way of the Pasteur method (as well as by chiral HPLC as described below). In particular, Apotex alleges that the compound would be recognized as weakly basic (and thus would readily form a salt with a strong chiral acid) and that it had a structural similarity to phenylglycine, a compound known to be resolved by the classic method.

[669] As explained by Dr. Adger and Dr. Davies, the Pasteur method involves three (3) steps:

- First, the racemic mixture is dissolved in a solvent and is mixed with a chiral resolving agent. For basic compounds, like PCR 4099 (due to the N in the pyridine ring), the chiral resolving agent will be an optically active (single enantiomer) acid. A reaction then occurs between acid and the base (*i.e.* PCR 4099) to form two distinct salts called diastereomers.

- Second, the diastereomers are separated from each other, normally by exploiting a difference in the solubility of the two diastereomers and retrieving the crystals of the diastereomer that are less soluble and thus precipitate out of the solution first.

- Third, each diastereomer is mixed with a base to release the separated enantiomer.

[670] Relying on Dr. Adger and Dr. Davies, Apotex further contends that the skilled person would follow a systematic approach to choosing the chiral acid, which was well-described even in the textbooks of the day. This approach involved (a) selecting a number of available chiral acids as resolving agents; (b) selecting a solvent in which to carry out the reaction; (c) preparing diastereomers with each of these acids in parallel experiments; and (d) monitoring and evaluating the results of the reaction.

[671] Apotex also relies on the literature and argues that, if a skilled person follows this rational approach, the resolution of organic compounds can be affected with a high probability of success.

[672] In addition, Apotex submits that because PCR 4099 is weakly basic, the skilled person would know to choose strong chiral acids as resolving agents for the screen. These agents would definitely include l or d-camphor-10-sulphonic acid, and perhaps tartaric and maleic acid because these were inexpensive, commonly available in laboratories, and were known to be strong acids. Work by Jacques, Collet and Wilen corroborates Dr. Adger's view in this regard. In particular, the text identifies $_{l}$ or $_{d}$ - camphor-10- sulphonic acid amongst those which have been used to effect successful diastereomeric salt resolutions of amines in the past.

[673] Although the Pasteur method was well-known and that there were four (4) methods to separate the enantiomers, Dr. Davies explained that in 1987, before the single enantiomers were separated, it was not possible to predict the properties (*i.e.* the physical properties, the pharmacological properties of activity, absorption, metabolism and excretion, or the toxicity profile) of the separated enantiomer based on the properties of the racemate. It is only after the enantiomers are tested that one can know whether an isolated enantiomer would have advantages over the racemate and the other enantiomer, and possess all of the properties to be useful as a drug (E.J. Ariëns, W. Soudijn, P.B. Timmermans, "Stereochemistry and Biological Activity of Drugs" (Oxford: Blackwell Scientific Publications 1983) at 89 to102).

[674] Dr. Davies also explained that there are several reasons for this unpredictability. Enantiomers can differ in pharmacological efficacy because they can be absorbed differently, metabolized differently, excreted differently, and they can interact in several ways with various biological receptors. Nobody can be reasonably certain which receptors will be involved with these processes, or how the different enantiomers will interact with them. One can never be reasonably assured ahead of time that any of those properties will differ to such a degree as to be clinically relevant.

[675] Dr. Davies mentioned that the skilled person could be deterred from resolving PCR 4099 because the presence of the ester functionality next to the nitrogen (the amine group) could cause the separated enantiomer to racemize back to PCR 4099 in the presence of stomach acid. However, Dr. Shebuski opined that the racemization could be avoided with enteric coating. Dr. Davies had never heard of enteric coating. Dr. Davies also explained that while the choice of a good resolving

agent remains mostly a matter of guesswork or of perspicacity, there are nevertheless some instances where the chemist can operate less blindly than in the past (Samuel H. Wilen et al, "Strategies in Optical Resolutions" (1977) Tetrahedron 38, at 2725-2736).

[676] On the basis of the evidence adduced, the Court agrees with Sanofi that, until the POSITA had first separated PCR 4099 into its enantiomers, it could not have tested the separated enantiomers and, only upon testing, could they have first learned that:

- Clopidogrel had antiplatelet aggregation activity;
- This activity was not present in the levo-rotatory enantiomer;
- Clopidogrel was better tolerated than the levo-rotatory enantiomer; and
- The bisulfate salt of CL was more stable than other salts.

[677] The Court nonetheless agrees with Apotex that the person of ordinary skill in the art would be led towards choosing the Pasteur method over the three other potential methods. But in the overall context at issue, Apotex has failed to convince the Court that the separation of enantiomers was straightforward in every case especially in the mid-1980s. In sum, Apotex has failed to convince the Court that the long existing Pasteur method would have worked.

(ii) Would Persons of Ordinary Skill in the Art turn to this Chiral HPLC?

[678] The second potential method for racemate separation was chiral HPLC.

[679] Apotex contends that by 1986-1987 a skilled person would also have known how to resolve PCR 4099 using chiral HPLC without difficulty or inventiveness.

[680] What is chiral HPLC? Dr. Wainer explained that in chiral HPLC the racemic mixture to be resolved is dissolved in a liquid called the “mobile phase”. The mobile phase is passed through a column which has been packed with chiral material, known as the “the chiral stationary phase”. The two enantiomers of the mixture interact differentially with the chiral stationary phase and, as a result, one of the enantiomers proceeds faster down the column than the other. Successive samples of what elutes from the column are collected during the period of the separation. Samples of the eluent, collected during the period the first enantiomer elutes, will contain that enantiomer. Similarly, samples of the eluent collected during the period the second enantiomer is eluting will contain the second enantiomer. Similar samples can be combined and extracted to yield the individual enantiomers.

[681] Dr. Wainer opined that the skilled person in 1987 would resolve PCR 4099 using chiral HPLC and would choose chiral HPLC and an AGP column for the separation of the enantiomers, due to the known chemical properties of PCR 4099:

- a steriogenic center in close proximity to an ester group;
- a phenyl ring and a pyridine ring flanking the chiral centre;
- a tertiary amine functionality; and
- its small size.

[682] The evidence at trial established that HPLC columns were available in 1986-1987 and could be used for two purposes: analytical and preparative. The question is whether at the relevant time HPLC columns were efficient.

[683] Dr. Davies testified that in 1986-1987 HPLC columns were only practically useful as an analytical technique not as a preparative technique. Hence, while it could be possible to separate

racemic material with analytical HPLC columns, the quantities separated would be extremely small (*i.e.* micrograms as opposed to grams) and could not be used on a commercial scale. Dr. Davies further testified that if HPLC was used on the analytical front it was not used massively. There were some commercial columns available, but they were very expensive and fragile. Mr. Badorc, for his part, testified that preparative HPLC columns were simply not available at Sanofi in the relevant time period.

[684] Apotex highlights a paper authored by William H. Pirkle and Thomas C. Pochapsky, "Chiral Stationary Phase for the Direct LC Separation of Enantiomer in Advance" (1987) 27 Chromatography stating that HPLC had reached "prominence" in both analytical and preparative separation of enantiomers. Dr. Davies was of the view that the word preparative was more of a promise. He did not recall any pharmaceutical company that he came across or any of his academic colleagues that were using the preparative HPLC column at the relevant time (Davies, T4621). In light of the overall evidence on the use of analytical and preparative columns for the separation of enantiomers, the Court accepts Dr. Davies' testimony in this regard.

[685] However, while at Smithkline in 1984-1985, Dr. Adger obtained sufficient quantities of single enantiomer for pharmacological testing using HPLC (Adger, T1694-1695). But, this event remains an isolated one and the evidence does not support the argument that by 1986-1987 the HPLC preparative column had become widespread.

[686] On the basis of the evidence, the Court has accordingly not been persuaded that HPLC columns had become common and widespread for the preparative separation of enantiomers. At

most, the evidence demonstrates that HPLC columns were available at the relevant time but limited to an analytical capacity producing insufficient quantities of a given separated racemic material. Thus, the Court finds that the POSITA would not have chosen this method in November 1987 to separate the enantiomers.

(iii) Conclusion on Methods to obtain Separation

[687] Thus, the question boils down to whether it was self-evident to a person of ordinary skill in the art that choosing one of the four (4) methods to separate ought to work.

[688] The evidence shows that only four (4) methods were available to separate the enantiomers. They are the following:

- the mechanical separation of crystals;
- the Pasteur method (resolution by formation of diastereomers);
- the preparation of pure enantiomers by asymmetric synthesis or asymmetric transformation; and
- the chiral HPLC.

[689] The Court agrees with Apotex that the mechanical separation of crystals would have been discarded by a person of ordinary skill in the art as it is considered a cumbersome process that is only applicable in limited circumstances where the racemic mixture is a conglomerate. Asymmetric syntheses, likewise, would not have been a first choice due to its difficulty and the fact that it produces a single enantiomer in circumstances where each enantiomer is required for testing.

[690] This would leave two (2) methods to choose from for separating the enantiomers: the Pasteur method (diastereomeric salt formation) and the chiral HPLC. Even though there were a

small number of methods available to the POSITA, Apotex has failed to convince the Court that, on a balance of probabilities, it was self-evident that these methods "ought to work".

[691] Indeed, the fact that the Pasteur method has existed for over 100 years guarantees in no way a particular result especially when the compound is separated for the first time, which was the case of PCR 4099. As for chiral HPLC, it was clear that in the relevant time period it was not available to produce the quantities necessary for further testing.

[692] Moreover, it is only after the enantiomers are tested that one can know whether an isolated enantiomer would have advantages over the racemate and the other enantiomer, and whether it would possess all of the following properties:

- clopidogrel had antiplatelet aggregation activity;
- this activity was not present in the levo-rotatory enantiomer;
- clopidogrel was better tolerated than the levo-rotatory enantiomer; and
- the bisulfate salt of CL was more stable than other salts.

[693] Thus, although there were a limited number of methods available to the POSITA and they would be directed to two (2) methods in particular, it was not self-evident on this basis alone that these methods of separation ought to work.

(b) Methods to Obtain Salt Formation

[694] However, with respect to the selection of the salts, the Court is of the opinion that it was a well-known and well-established methodology at the relevant time and that it would have been self-evident that the method to obtain salts ought to work.

[695] A salt will form when a reaction is created between an acid and a base. If a compound is basic, an acid would have to be chosen. If the compound is weakly basic, a stronger acid would have to be chosen and so on. The formation of the salts occurs when an acid and a base react. Typically, a “salt screen” is prepared which amounts to the preparation of salts with various different acids in parallel so that the salts that crystallize from solution can be quickly identified.

[696] In this case, the evidence demonstrates that clopidogrel is weakly basic. Consequently, a strong acid would be required to form a salt. Sulfuric acids and hydrobromic acids are strong acids and would be used for the formation of salts. Dr. Adger explained that this procedure is known as the pKa rule of 2.

[697] More particularly, pKa is the acid dissociation constant at logarithmic scale. It refers to the tendency of a given molecule to donate a proton or hydrogen group. The lower the pKa, the stronger the acid. When the difference in pKa between the acid and base is greater than 2, a strong salt can be expected to form (Byrn, cross T3041; Byrn Report, paras 28-29). The pKa of clopidogrel was reported as 4.55 (Byrn, cross T3076).

[698] Dr. Adger and Dr. Byrn agreed that sulfuric acid would be the first or one of the first acids to be included in the screen in making pharmaceutical salt in 1987.

[699] Mr. Badorc also agreed that strong acids were chosen because they provided a good chance of forming crystalline salts (Badorc, cross T4192-4195).

[700] Dr. Adger opined that making salts is a routine part of pharmaceutical development and commonly used pharmaceutically-acceptable salts have been available in the literature since 1977, when an article entitled “Pharmaceutical Salts”, 66 J. Pharm. Sci 1-19 (1977), also known as the Berge list, was published.

[701] However, Dr. Byrn testified that forming a salt was always novel and always inventive because it is “completely unpredictable”:

> …But it’s unpredictable, and you can’t be sure that will work. So you can’t just limit it. You can’t say, “Oh, I have a strong base, so I am going to use only weak acid”. You have to use all of the possible acids and bases, and Berge is the one that’s used for this typically, and he lists 80 different acids and bases as possible salt formers, so the – and then there are many – pardon me, lists 80 acids. Clopidogrel is a base, so he lists 80 acids. If it happened to be an acid, we’d be interested in the bases because, remember, a salt is a reaction of an acid and a base, so since clopidogrel is a base, we react it with 1 of the 80 acids.
>
> (Byrn, T2852-2853).

[702] Further, relying on articles in the field of salts, Dr. Byrn opined that the selection of the salt remains a difficult choice (see Stephen M. Berge, Lyle D. Bighley & Donald C. Monkhouse, “Pharmaceutical Salts”(1977) 66 Journal of Pharmaceutical Sciences; Philip L. Gould, “Salt selection for basic drugs” (1986) 33 Int’l Journal of Pharmaceutics; P. Heinrich Stahl & Camille G. Wermuth, eds, Handbook of Pharmaceutical Salts, Properties, Selection, and Use (Zurich: Verlag Helvetica Chimia Acta, 2002).

[703] Overall, the Court prefers Dr. Adger’s approach to Dr. Byrn’s. The evidence clearly demonstrates that salt selection was present in the literature. More particularly, the Berge list refers

to eighty (80) acids for forming salts with drug compounds that are basic and twenty-one (21) bases are listed for forming salts with drug compounds that are acidic. The fact that clopidogrel was a weak base would lead the person of ordinary skill in the art to choose a strong acid and both experts agreed that sulfuric acid would be at the top of the list.

[704] Mr. Badorc himself provided evidence to the effect that methods for obtaining salts were well-established. Indeed, Mr. Badorc testified that he was cognizant of the pKa rules of 2 when he decided to form salts of clopidogrel. He also acknowledged selecting the acids for salt formation based on the well-known Berge list.

[705] Mr. Badorc further testified that although bisulfate salt was not listed on the FDA list it was listed on the non-FDA list. Mr. Badorc also admitted that he knew about the non-FDA list and that the non-FDA list was approved in France at the relevant time and that he had access to this list.

[706] For all of these reasons, the Court accordingly finds that the few methods to obtain salt formation were well-known and a well-established methodology at the relevant time.

(c) Conclusion: “Ought to Work”

[707] The Court therefore finds that at the relevant time, the Pasteur method could not guarantee a specific result and the chiral HPLC method could not produce sufficient quantities of the separated racemic material and was not yet widespread. However, on the basis of the experts’ testimony and the inventor’s own admissions, the Court concludes that the methods for salt formation were readily available and commonly used to make pharmaceutically acceptable salts.

[708] Thus, the Court is of the opinion that, while it was not clear that it was self-evident to the POSITA that the methods of separation ought to work, it was clear that the method of salt preparation would work.

(2) What is the extent, nature and amount of effort required to achieve the Invention? Are Routine Trials carried out or is the Experimentation prolonged and arduous, such that the trials would not be considered routine

(a) What is "Routine" in separating the enantiomers of PCR 4099 and obtaining the salts

[709] The Court finds that the POSITA would have been directed towards the classic Pasteur method to separate. In turning to this method, based on the evidence, the Court is of the opinion that the method was routine.

[710] Sanofi argues that the definition of routine does not encompass inventive work which amounts to making a new compound for the first time. Sanofi further alleges that the first time any experiment is conducted there is uncertainty as to the result because one does not know if the experiment will work as hoped or what the result will be. This is in contrast to what is truly routine, namely an experiment that has been performed many times before with the same components and under the same conditions, each time giving the same result (e.g. regulatory quality control testing).

[711] Sanofi also submits that its definition of "routine" is consistent with the meaning ascribed to this notion by the Supreme Court of Canada in *Plavix*. In that case, the Supreme Court of Canada noted that there were known methods for separating racemates and known methods for testing the properties of the enantiomers and salts. However, it was found that such experimentation was not

routine. Thus, for Sanofi, using known techniques to identify something that was previously unknown is unobvious.

[712] More specifically, Sanofi maintains that the evidence clearly establishes that it was not obvious that one could successfully separate PCR 4099. Even if PCR 4099 could be separated, it was far from obvious that advantages would result from the separation. Frequently one would either get no benefit, for instance in the case where the activity and toxicity are the same as between the enantiomers or where there is racemization *in vivo*.

[713] Dr. Adger generally agreed that drug discovery is never certain. However, some process to obtain a drug can sometimes be easier than others. Dr. Adger mentioned that it is never a trivial matter.

[714] Dr. Byrn discussed the fact that salts including salt screen involve a level of difficulty and, in some cases, will not necessarily work.

[715] Against this background, the Court observes that Sanofi appears to suggest that making a new compound for the first time amounts to an invention. This cannot be so. The making of a new compound for the first time cannot be an invention all the time. It remains a question of fact to be assessed on a case-by-case basis.

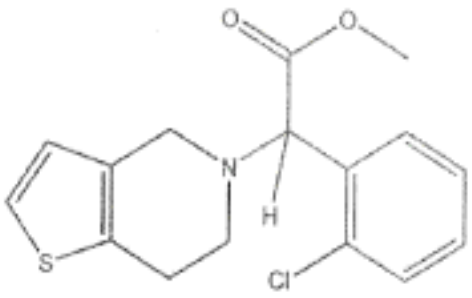
[716] Specifically, based on the evidence tendered, the Court cannot agree with Sanofi because the work of Jean Jacques, André Collet & Samuel H. Wilen in a 1981 publication *Enantiomers,*

Racemates, and Resolutions (p 384), indicates that ethanol, methanol or acetone were solvents most commonly used in diastereomeric salt resolution (Pasteur method).

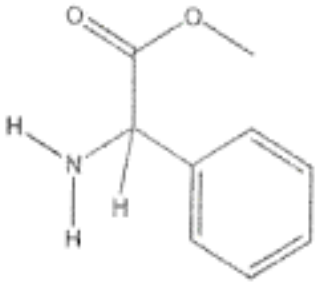
[717] The Court agrees with Apotex that the literature confirms that camphozxcr-10-sulfonic acid and tartaric acid had been used to resolve phenylglycine and its methyl ester. Indeed, there are precedents in the literature. For instance, as early as 1925, A. W. Ingersoll reported the resolution of phenyglycine by diastereomeric salt formation using camphor-10-sulphonic and the resolution of the methyl and isopropyl esters of phenyglycine was achieved by John C. Clark in 1976 using tartaric acid. The Court notes that Dr. Davies did not challenge Dr. Adger's comments regarding the precedents for the diastereomeric salt resolution.

[718] The evidence also demonstrates that Phenylglycine Methyl Ester has a similar structure to PCR 4099 (P-154):

PCR 4099



Phenylglycine Methyl Ester



[719] The skilled person would be expected to know about this. Indeed, Dr. Davies was of the view that a "chemist has to know everything that is in the literature in the area that he is working"

and Dr. Adger recalled the simple reality that "… spending a day in the library can save you a week in the lab …" (Adger, T1561-1562).

[720] The skilled person would thus review the literature and, based on other experiments, would find out that there is a "guide". On the basis of the existing literature and the previous work on Phenylglycine, the Court is convinced that the resolution of PCR 4099 would be accomplished by the skilled person using the diastereomeric salt resolution methodology and this would have been routine.

(3) Is There a Motive provided in the Prior Art to find the Solution the Patent addresses?

[721] When assessing whether a motivation was provided in the prior art, the Court will look as to whether there is more than a mere possibility in this regard. This approach was explained by the Federal Court of Appeal in *Pfizer Canada Inc. v Apotex Inc.*, above.

(a) Motivation to separate: the "Mumblings" of the Mid-1980's

[722] Was there a motivation to separate the enantiomers of PCR 4099 in 1987? This issue sparked an interesting debate between the parties.

[723] While there were undoubtedly discussions on the issue of separating enantiomers in the scientific community in the mid-1980's, the real question is whether these discussions had reached such a level that the person of ordinary skill in the art working in the field in 1987 would have been motivated to separate the enantiomers. Was there an understanding that regulatory agencies would have expectations or/and requests in that regard? Had these expectations turned into policies?

[724] In this connection, the Court must consider the key events in chronological order until the relevant time which fed into the "mumblings" surrounding the separation of enantiomers and then assess whether the intensity of the "mumblings" was such that it may have led to a motivation to separate the enantiomers of PCR 4099.

Event 1: The Thalidomide Disaster

[725] Thalidomide was a compound approved and administered in Europe and in the United Kingdom in the late 1950's. It was widely used in Europe for conditions that were associated with morning sickness experienced by pregnant women. But thalidomide had a teratogenic property with one of the less active isomers. Consequently, many infants were born with severe birth defects as a result of their mother having taken thalidomide. Dr. Sanders referred to thalidomide as the "thalidomide disaster". He testified that, as a consequence, the principles of stereochemistry in biological systems, and examples of stereoisomers that differed markedly in pharmacological and toxicological action (e.g. thalidomide), were well known to toxicologists well before 1988.

[726] Dr. Wainer explained that applications were made in the United Sates for thalidomide. However, Dr. France Oldham Kelsey, an FDA review pharmacologist, refused to allow thalidomide in the United Sates and blocked the sales of thalidomide. Dr. Wainer testified that Dr. Kelsey made that decision based on the literature and thought that "something was not right about thalidomide". Thalidomide was thus prevented from entering the American market.

Event 2: The 1985 Japanese Guidelines

[727] Dr. Wainer testified that in 1985, Japanese regulators adopted and published pharmaceutical manufacturing guidelines directing sponsors of applications for racemic drugs to separate and characterize the enantiomers (Wainer Report, Tab 23). These guidelines provide that "[d]epending on the type of pharmaceutical substances, there are times when the results of other additional antigenic tests may be required. Hence, if it is known that the pharmaceutical substance has special antigenic properties or causes adverse reactions due to such antigenic properties, an investigation and study of those properties, at the very least, should be conducted".

[728] Dr. Davies stated that he wasn't aware of the Japanese guidelines being published, but he knew of their existence and agreed, on the basis of an earlier statement in a proceeding in the United States, that there were discussions about the Japanese document in the scientific community in 1985 (Davies, cross T4565).

Event 3: Dr. Kumkumian's 1986 Speech

[729] Dr. Wainer opined that by 1986, the FDA had come to expect that sponsors of racemic drugs were to resolve and characterize the pharmacological and toxicological properties of racemic drugs and that the excuse that this was a difficult task would no longer be accepted.

[730] In March 1986, a major scientific international meeting - the 133rd Annual Meeting of the American Pharmaceutical Association in San Francisco, California - was attended by thousands of participants working in the drug development community. Dr. Kumkumian, Assistant Director of Chemistry at the FDA at that time, declared in a speech before a very large audience that sponsors

of applications for racemic drugs in the United States were expected to discuss the results of studies carried out to investigate the physical, chemical and biological properties of single enantiomers. Dr. Wainer, who worked at the FDA at the time and participated at the conference, provided the Court with the context surrounding the Kumkumian speech.

[731] In his speech, Dr. Kumkumian stated the following:

> Many chemicals that exist contain stereoisomers and in which biochemical differences have been shown among these isomers. In glutamic acid, for example, only the dextrorotatory isomer functions as the well known flavor enhancing agent. In aspargine, only the dextro isomer is sweet. In regard to the well-known drug chloramphenical, only one of the four isomers acts as an antibiotic. The differences in behavior of enantiomers in living matter are explainable by the fact that reactions in living matter are catalyzed largely by optically active enzymes or need to compliment stereospecific receptors…
>
> As we are aware specific isomers may not only have quantitative differences in comparable activity with their "opposite" isomers but do, in some instances, have qualitatively different pharmacologically, therapeutically and pharmacokentically. Of the four stereoisomers in propoxyphene, only the dextro isomer of the alpha racemate exhibits analgesic properties in contrast to the levo form which is marketed as an antitussive agent.
> (Page 7)
>
> As we can see from these examples, individual stereoisomers can have various effects for their counterpart isomers in a drug molecule consisting of a racemate. These considerations should be addressed in evaluating the safety, effectiveness and quality of the drug product.
> (Page 9)
>
> Whether a sponsor of an IND decides to go with a specific isomer or a racemate it should be clearly delineated in the original submission. The data submitted on substances that do or can exist as stereoisomers should include a discussion of the possible isomers which may result from the method of the manufacture and the results of studies carried out to investigate the physical, chemical and biological properties of these isomers.
> (page 12)

> (Kumkumian, Charles. "Regulating the Enantiomeric Purity of Pharmaceuticals: The FDA's Point of View", presented at the 133rd Annual meeting, American Pharmaceutical Association, San Francisco, California, March 19, 1986)
>
> [Emphasis added]

[732] This above-quoted statement by the Assistant Director of the FDA's Office of Drug Research and Review intended to send a message to a large audience: the FDA wanted racemic drugs to be resolved and their enantiomers characterized. By these remarks, the FDA was providing information about its direction in the future. This direction, crafted in the 1987 FDA guidelines, would eventually crystallize and become the FDA policy in 1992.

Event 4: The 1987 FDA Guidelines Document and the Stereoisomer's Committee

[733] Dr. Weissinger testified that, due to some confusion with respect to the stereoisomers policy, she was asked to co-chair a committee with Dr. Kumkumian and draft a policy for the FDA regarding these compounds. The stereoisomers committee was set up in 1989. The same year, Dr. Weissinger wrote a paper informing the pharmaceutical community that the FDA "was going to come up with a policy and that we were meeting to do this and we had a new committee and what the committee's charge was" (Weissinger, T2580-2582).

[734] The stereoisomers committee conducted an evaluation and eventually Dr. Weissenger wrote what would become the 1992 FDA policy.

Event 5: The 1989 Nature Article and the Pressure for New Drugs

[735] It is worth noting that in 1989 (two years after the relevant date at issue in this case), in the leading and well-respected scientific journal *Nature* (vol. 342 no.6250), Dr. Davies wrote that "the

differing pharmacological effects of the two enantiomers of chiral molecules are now well documented". He added: "[w]e are at the watershed of asymmetric synthesis – in the near future it will be common practice to synthesize all potential new drugs as single enantiomers and there is already pressure from regulatory agencies in this direction" [Emphasis added]. This statement is in large part a reiteration of Dr. Kumkumian's speech.

[736] Also, the Court agrees with Dr. Davies that, as a whole, the literature did not suggest to an ordinary chemist in 1987 how to obtain the enantiomers. The writings of Dr. Davies in 1986 and 1987 seem to suggest that there was recognition that enantiomers of a molecule could have different effects. For instance, Dr. Davies wrote in 1986 that "it is now recognized widely that the two enantiomers of a molecule can have a different *in vivo* effect. For this reason, the search for novel, more efficient and, most importantly, more general methods for the synthesis of enantiomerically-pure organic compounds is intensifying" (Asymetric synthesis – Prospects for industry: Stereoselective synthesis via arene chromium tricarbonyl complexe, 1986 p 173) [Emphasis added]. He also wrote in 1987 that there was a "growing appreciation of the different biological effects of enantiomeric molecules".

[737] On the basis of the above, and considering that published papers or articles are generally submitted six (6) months to a year prior to publication, the Court concludes that leading chemists in the area of drug discovery were aware in 1989, or before, that "there is already pressure from regulatory agencies [toward separation]" [Emphasis added].

Event 6: Joint Venture Partner Asking about Data on Enantiomer

[738] In the mid-1980's, Sanofi was involved in a joint venture with certain Japanese companies. Of interest is an internal Sanofi letter dated September 29, 1986, which was sent to high-ranked individuals including Mr. Pierre Simon. This letter consisted of a request from the Japanese Joint Venture and specifically concerns the enantiomers of PCR 4099. It mentions the following on p. 2 at B. under the heading Health Authorities: "within the context of the Japanese Joint Venture, we have been asked for "separation and study enantiomers" without further details" [Emphasis added].

[739] This same letter also makes reference to a similar request from the FDA:

> MEIJI-SEIKA and TAISHO have been told that the work is in progress on these enantiomers. But they have not been sent any report. Regarding the FDA, the telex from A. URDANG (Sept. 16. 1986) queried on this subject by W. CAUTREELS, is in the same vein.

[740] At trial, Dr. Maffrand did not provide any further explanation regarding the above-quoted paragraph. He testified in cross-examination, that he did not know A. Urdang and that the telex referred to in the letter was requested in the American proceedings but was never located.

Event 7: The 1992 FDA Policy In Force

[741] Dr. Weissinger testified that the FDA policy on stereoisomers came into force on May 1, 1992, and that prior to 1992, there was no coordinated policy on how to handle stereoisomers drugs.

[742] Therefore, the FDA's 1992 policy would signal a long-term change in the pharmaceutical landscape, as this new policy generally required that all new chiral drugs be tested to determine if a pure isomer form would eliminate unwanted side effects.

(b) Summary

[743] On the basis of the evidence, the “mumblings” with respect to enantiomers and their different effects started in the early 1980’s and clearly intensified in the mid 1980’s. While it is true that the FDA policy was crystallized with its release in 1992, nevertheless, stereoisomers were a topic of interest in the mid 1980’s. The 1992 FDA policy represents the final outcome of discussions and changes that were well underway in the 1980’s. Hence, the Court is of the view that the 1992 FDA policy does not represent the beginning of knowledge and awareness. Prior to 1992, there were important milestones and clear indicators that the landscape was already shifting.

[744] As early as 1985, the Japanese regulators had published pharmaceutical manufacturing guidelines. The same year Sanofi was told by way of a letter received from a joint venture partner that the Japanese regulators were inquiring into separation of the enantiomers. This same letter also made reference to a similar request by the FDA. Although the telex regarding that letter could not be found, the fact remains that a Sanofi document refers to the regulatory requests from Japan and the United States regarding the separation of enantiomers.

[745] Also in 1986, Dr. Kumkumian made an important presentation to a large audience and outlined the expectations of the FDA for the years to come – *i.e*. that the properties of enantiomers would likely become a requirement for the regulatory process. Dr. Wainer, who worked at the FDA until 1986, testified with respect to the change of culture and the expectations within the FDA in the mid-1980s.

[746] The evidence shows that in the mid-1980's, there were clearly discussions and heated debates with respect to the separation of enantiomers. In an article published in 1987, authors stated in the Journal of Medicinal Chemistry that "there were great interests in investigating enantiomers" (P-178). Likewise, Dr. Maffrand testified to the fact that although there were no formal regulations in place, there were discussions in this regard amongst the health authorities in the United States. Dr. Maffrand added that although it was not a major element in deciding to separate the PCR 4099 enantiomers, it was nonetheless taken into account. In addition, Dr. Maffrand stated that the discussions were occurring in the scientific community before the decision to separate the enantiomers of PCR 4099 was made (Maffrand, T4928):

> Q. And those discussions in the scientific community were ongoing at the time you made the decision to separate the enantiomers of 4099. Is that correct?
> R. Oui, c'est ce que j'ai dit. Mais elles existaient déjà depuis plusieurs années.

> Q. And those discussions in the scientific community were ongoing at the time you made the decision to separate the enantiomers of 4099. Is that correct?
> A. Yes, that's what I said. They existed for a number of years already. They had been going on for a number of years.

[747] Dr. Davies suggested that drug companies would avoid resolving racemates for fear of finding a better compound but, in light of the overall evidence, the Court does not accept Dr. Davies' testimony on this point. Significantly, it is inconsistent with the fact that Sanofi was already resolving enantiomers during this period – e.g. PCR 1033 and PCR 3549.

[748] It is accordingly difficult to conclude that a person of ordinary skill in the art would not have been aware of the on-going discussions which were taking place on the issue in the mid-1980's,

unless it deliberately chose to ignore them. At the very least, in 1986-1987, there was a clear indication that the separation of enantiomers could be performed and it was therefore important to test for them in order to pre-empt what was to come.

[749] It follows that although the FDA's official policy was released in 1992 and that the document entitled "1987 FDA Guidelines" was never published or circulated, the evidence indicates that the literature, Dr. Kumkumian's speech, the expectations of the Japanese regulators, and the intense growing "mumblings" around stereoisomers, all reflected the content and spirit of the 1987 FDA guidelines at the relevant point at issue. The discussions and the expectations in the scientific community had reached the level where the line was drawn in the sand. At the relevant date, the paradigm had shifted.

(c) Conclusion: "Motivation"?

[750] For all of these reasons, the Court finds that the person of ordinary skill in the art would therefore have had the motivation to separate the enantiomers of PCR 4099. In reaching this decision the Court is aware that it has to remain cautious that "obviousness" does not provide disincentive for innovation (SCC *Plavix*, paras 64-65).

[751] The Court will now address what was the actual course of conduct that culminated in the invention.

(4) Actual Course of Conduct that Culminated in the Invention

[752] Dr. Maffrand was not named as an inventor of the patent but it was Dr. Maffrand's idea to separate the enantiomers of PCR 4099. He asked Mr. Badorc and Dr. Fréhel to separate the enantiomers (Maffrand, T4792-T4793).

[753] Although not raised as an issue in this case, the Court questions whether Dr. Maffrand should have been named as an inventor in the '777 Patent. However, this issue is not before the Court and will not be addressed in this case.

[754] Mr. Badorc obtained a diploma of technology in chemistry in 1972 at the Université de Rennes in France, where he learned the diastereomeric salts method of separation. Separating the enantiomers of PCR 4099 was not Mr. Badorc's first separation of a compound. He had previous separation experience with other compounds – namely PCR 1033.

PCR 1033

[755] In 1975, PCR 1033 was tested for antiplatelet aggregation activity and it appeared that PCR 1033 could be considered as a candidate for development as antiplatelet aggregation agent. However, based on the pharmacological studies, the observed toxicity appeared to be worse than that of ticlopidine. Therefore, it was decided that PCR 1033 was not a good candidate for further development.

The Enantiomers of PCR 1033: PCR 3071 and PCR 3072

[756] In 1978, Dr. Maffrand asked Mr. Badorc to separate PCR 1033 using the diastereomeric salt resolution. Using the diastereomeric salt resolution for the first time, a technique learned at Université de Rennes, Mr. Badorc was rapidly successful in his first attempt and separated the enantiomers of PCR 1033. He began working on June 16, 1977 and completed the work on June 17, 1977. The levo-rotatory enantiomer was called PCR 3071 and the dextro-rotatory enantiomer was called PCR 3072. It was later found that PCR 3071 was less well-tolerated than ticlopidine and could not be administered to humans. The development of PCR 3071 therefore ceased.

PCR 3549

[757] Also in 1978, Mr. Badorc synthezised the ethyl analog of ticlopidine, which was called PCR 3233. PCR 3233 was an oily base, but Mr. Badorc was able to make a crystalline nitrate salt, which was called PCR 3549. Dr. Maffrand asked Mr. Badorc to obtain the enantiomers for PCR 3549. However, Mr. Badorc failed to separate PCR 3549 using diastereomeric salt formation, which was the same technique used to separate PCR 1033. Mr. Badorc decided to try another technique called asymmetric synthesis. Two enantiomers (PCR 3620 and PCR 3621) were obtained from PCR 3549 using asymmetric synthesis.

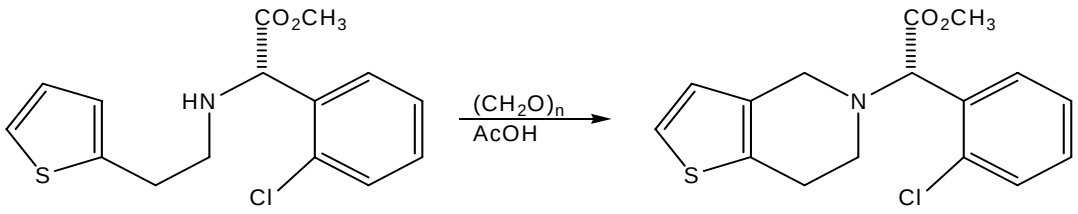
[758] Based on an apparently favourable activity/toxicity ratio, Dr. Maffrand formed the view that PCR 3549 should be developed as a drug candidate. However, given toxicity issues in animals and lack of sufficient therapeutic activity, the development of PCR 3549 was abandoned.

Resolution of PCR 4099

[759] Mr. Badorc stated that Dr. Maffrand made the decision – perhaps with Sanofi's Research division – to separate the enantiomers of PCR 4099. In all there were three (3) attempts to resolve PCR 4099.

[760] First, Mr. Badorc and Dr. Fréhel decided that an asymmetric synthesis similar to the one used to obtain the enantiomers of PCR 3549 would have a greater chance of success for PCR 4099 than trying to separate the enantiomers via diastereomeric salt resolution as experienced with PCR 1033. Mr. Badorc indicated that this choice was preferred for fear of racemization (Badorc, T3936-3940). However, the Court observes that in a report dated June 12th, 1986 (PCR 4099 Resolution of R and S Enantiomers of PCR 4099) (P-161), authored by Mr. Badorc and Dr. Fréhel, there is no mention of any concern of racemization in using the diastereomeric salt method. Further, there is also no mention of racemization in Mr. Badorc's Canadian affidavit of June 2003 in the part describing the separation of PCR 4099.

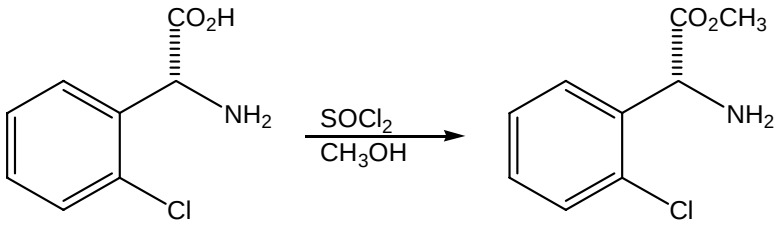
[761] In any event, the asymmetric synthesis route was chosen instead of the diastereomeric salt resolution. Mr. Badorc decided to synthesize only one enantiomer of an intermediate called OCBATH (cyclization instead of resolution) by starting with an enantiomerically pure precursor molecule and then converting that intermediate into one of the enantiomers of PCR 4099 according to the following alkylation reaction:



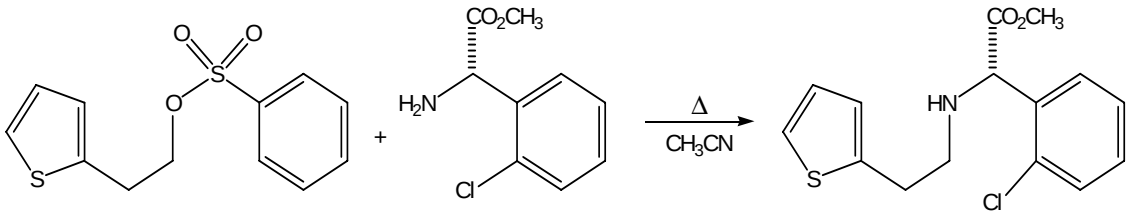
Dextro-rotatory or Levo-rotatory enantiomer of OCBATH

Dextro-rotatory or Levo-rotatory enantiomer of PCR 4099

[762] On November 12, 1985, Mr. Badorc first synthesized the dextro-rotatory enantiomer of methyl-2-chlorophenyl-glycinate. He then synthesized the levo-rotatory enantiomer. Both syntheses were done according to the following condensation reaction scheme:



[763] This enantiomerically pure product was then used in the following reaction:



[764] These experiments yielded the OCBATH compound. However, analytical results indicated that the alkylation reaction had led to a racemization, giving Mr. Badorc the racemic OCBATH compound instead of the single enantiomers he was seeking. This route to synthesis was therefore abandoned.

[765] Secondly, Mr. Badorc decided to synthesize the PCR 4099 enantiomers by resolving the racemic OCBATH compound by making disatereomeric salt with a chiral acid, followed by fractional recrystallisation. Mr. Badorc was successful in yielding a salt from one of the enantiomers of the OCBATH compound. However, Mr. Badorc explained that when he tried to cyclize the enantiomers of the OCBATH in order to get the corresponding enantiomers of PCR 4099, he obtained racemic PCR 4099 in both cases. This approach was also abandoned.

[766] Mr. Badorc then turned to a precursor of PCR 4099, PCR 3068, but the separation did not succeed. Mr. Badorc then reverted to PCR 4099 for a third attempt.

[767] Having failed with two previous attempts at asymmetric synthesis on PCR 4099, Mr. Badorc decided to attempt a separation of the enantiomers by formation of diastereomeric salts, the same technique used to separate PCR 1033 which was successful for PCR 1033 but had initially been discarded for PCR 4099. Mr. Badorc testified that the decision to use an acid was risky, because acid can racemize the enantiomers (Badorc, T3950-3952). By combining acid and solvents, a gum formed. Mr. Badorc testified that he set up a series of tubes containing different quantities of dextro-rotary camphor-10-sulfonic acid with different solvents. He then sealed the tubes and he waited one month before any crystals formed. He then added 0.4 equivalents dextro-rotatory camphor-10-sulfonic acid and after 48 hours a few crystals appeared. Following further manipulations, Mr. Badorc was successful in obtaining the enantiomers of the PCR 4099 on April 15, 1986.

[768] The biological department tested the individual enantiomers for activity. The tests revealed that the dextro-rotatory enantiomer of PCR 4099 had all the activity and the levo-rotatory was inactive. The levo-rotatory was also shown to be more toxic that the dextro-rotatory (*i.e.* clopidogrel).

[769] Next, Sanofi turned to the preparation of clopidogrel as a pharmaceutically acceptable salt. On July 3, 1987, Sanofi had three (3) salts: the camphorsulfonate, the hydrogen sulfate and the hydrobromide salts, each being considered for development. On August 11, 1987, Sanofi had tested the salts and determined that the hydrogen sulfate and camphorsulfonate salts were similar in physical and chemical stability and had better properties compared to the hydrobromide or the hydrochloride camphorsulfonate salts.

[770] The Court had the benefit of listening to Mr. Badorc for two (2) days. During these two (2) days, Mr. Badorc appeared to adjust his testimony constantly. Crucial portions of Mr. Badorc's testimony remained incomplete, inconsistent and to some extent left the Court puzzled. There are a number of discrepancies between the story told by Mr. Badorc to the Court and the documentary evidence, more specifically his laboratory notebook.

[771] The most important discrepancies that surfaced at trial are found in Mr. Badorc's laboratory notebook relating to the test tubes screens (otherwise known as the chemist's "secret garden").

Test Tubes

[772] Mr Badorc's laboratory notebook relates that on March 4, 1986, one equivalent of camphorsulfonic acid was added to PCR 4099 in ethanol. A gum was obtained in the experiment but no crystals were formed (Badorc, T4115). On March 18, 1986, 0.4 equivalent of camphorsulfonic acid was added to PCR 4099 in acetone and on March 21, 1986 crystals were obtained, which is confirmed by the entry for March 24, 1986 (Badorc, T4135).

[773] Mr. Badorc testified that he conducted a series of test tube screens. The problem with Mr. Badorc's testimony is that these test tubes screens were not recorded in his laboratory notebook and were not provided to the Court in any other documents. The test tubes screens are key to the difficulty of the work as alleged by Mr. Badorc, but his testimony in this regard was unpersuasive.

[774] Mr. Badorc told the Court that the reason for not recording the failed test tube experiments in his notebook is because he was ultimately successful. Mr. Badorc said that his laboratory notebook was the successful experiment. He also provided a peculiar reason in support of failing to enter the test tube screens in the laboratory notebook: the chemist's "secret garden" (Badorc, T4117). By virtue of this concept, the chemist would be exempt from recording failed attempts. Yet, in other instances, the laboratory notebook contains records of unsuccessful attempts at diastereomeric salt formation for PCR 4099. Mr. Badorc's explanation for not recording his experiments because they were failures when there was ultimately a successful experiment is thus unconvincing. It is contradicted by the fact that he recorded his March 4, 1986 experiment which was a failure. It is also contradicted by the fact that the failure with tartaric acid that was recorded for the attempted separation of PCR 3549 before recording the failures with other acids. In sum, Mr.

Badorc seemed to have varying subjective standards in terms of the experiments that would eventually find their way in his notebook. His explanation regarding these inconsistencies failed to convince the Court.

[775] Finally, it is noted as an *obiter* that Mr. Badorc's U.S. deposition makes no mention of the test tube trials and Mr. Badorc's evidence at trial was that these experiments started in February 1986. However, his evidence before the Canadian court in the NOC case, which was repeated in his Australian affidavit, was to the effect that these experiments were attempted in March 1986. This is a further discrepancy that weakens Mr. Badorc's credibility as a witness in this case.

[776] The Court also agrees with Apotex that Mr. Badorc's crystal clear recollection of unrecorded test tube trials, with precision as to the resolving agents, their amounts and the solvents, stands in stark contrast to Mr. Badorc's failed memory with respect to the attempted separation of PCR 3549. Unlike the test tube trials for PCR 4099, the separation work in the case of PCR 3549 was recorded in Mr. Badorc's laboratory notebook. Nonetheless, in 2003, under oath, Mr. Badorc had simply forgotten that he had attempted separation by diastereomeric salts and had successfully separated the enantiomers by asymmetric synthesis. He forgot the separation of PCR 3549, notwithstanding the fact that it was the first time that he had ever carried out an asymmetrical synthesis of an enantiomer. The Court does not accept that these discrepancies are trivial. Rather, they relate to a number of material points at issue in this case.

[777] Mr. Badorc also mentioned that he seeded the March 18, 1986 experiment with crystals from the second of the two screens. Again, this was not recorded in his laboratory notebook for the

March 18 experiments. Had it been recorded, it could possibly have corroborated the existence of the test tube experiments.

[778] There is also an issue with respect to the time dedicated to separating the enantiomers of PCR 4099. Mr. Badorc testified that it occupied the majority of his time during five (5) months. He also testified that he waited one month – mid-February to mid-March 1986 – before obtaining the first crystals. The computation of Mr. Badorc's fifty-five (55) days of work apart from the test tube screens are not listed in the laboratory notebook or on another list. There is no list of page numbers from the laboratory notebook in evidence allowing the Court to compute the fifty-five (55) days of work alleged by Mr. Badorc. The approximate and vague explanation provided by Mr. Badorc in this regard was unconvincing.

[779] Mr. Badorc also confirmed that he used camphorsulfonic acids which were taught by the work of Jacques and Collet and were commercially available acids. At the time Mr. Badorc performed the separation of PCR 4099, he believed that camphorsulfonic acid was the strongest acid:

> Q. Thank you. We talked about some of the chiral acids yesterday, and I think you mentioned also Jacques and Collet yesterday in your evidence. Am I right that at the time you were going to separate 4099, there was a list of optically active acids that was available, a list of commercial products?
> R. Oui, oui, dans tous les catalogues qui peuvent exister, Aldrich, Sigma, j'en passe, il y a la liste d'acides chiraux commercialement disponibles.
> Q. Okay. And of that list, would you say perhaps there were about a dozen optically active acids that would have been available to you?
> R. Je dirais, à l'époque, peut être bien à l'époque oui, même peut être plus ou peut être moins, je sais pas.
> Q. Okay.
> R. Mais il y avait des acides chiraux disponibles commercialement, qu'on voyait dans tous les catalogues, disponibles dans tous les laboratoires.

Q. Okay. And would I be correct that of those that were available to you, the strongest at the time that you were doing the separation was camphorsulfonic acid?
R. Non.
Q. Do you still have - I told you to put it away, so I'm sorry, but document number 7, the US trial, I would like you to go to page 1817. I would like you to go - do you have it, 1817? I think you have it, because it looks like you are reading. 1817, I would like you to go to line 11. You were asked the question by the Court on that occasion:

"What is the universe that you start with of optically-active acids? How many are in this list or lists that you are referring to?"

You say at line 14:

"I would say that perhaps there are about a dozen optically active acids, and the strongest being - now, I'm talking about the strongest at the time that we were doing this, was camphorsulfonic acid."[As read]

Were you asked that question by the Court and did you give that answer to the Court on February 7th, 2007 in the US trial?
R. C'est la réponse que j'ai donnée au tribunal, oui, parce que je pensais, j'avais mis l'acide toluyl tartrique et dibenzoyl tartrique dans la série de tubes, et c'est vrai que je pensais que le camphre sulfonique était le plus fort. Et c'est qu'après que j'aie regardé, j'ai vu de que l'acide toluyl tartrique, que je pensais un peu plus faible que l'acide camphre sulfonique, ne l'était pas. En fait, c'était le toluyl tartrique qui était le plus fort. Mais à l'époque où j'ai témoigné ça aux États Unis, je pensais que l'acide camphre sulfonique, oui, était plus fort que l'acide dibenzoyl tartrique. Et j'ai contrôlé après, et c'est en fait, l'inverse. C'est le toluyl tartrique qui est plus fort, après le dibenzoyl tartrique et après l'acide camphre sulfonique.
Q. So after the trial, you learned or discovered that the camphorsulfonic acid was not the strongest acid. You learned that after the trial; correct?
R. Après le procès, oui. Je savais que les autres étaient des acides forts, mais je pensais que l'acide camphre sulfonique, innocemment, était plus fort que l'acide dibenzoyl tartrique. J'étais un peu surpris, mais en fait, le plus fort, c'est le dibenzoyl tartrique.
Q. So up until the trial, your belief that the camphorsulfonic acid was the strongest acid, then, because that is the answer you gave to the Court?
R. Je le pensais, oui, je savais que les autres étaient des acides forts, mais je pensais que l'acide camphre sulfonique était plus fort.
Q. <u>When you did the separation of 4099, your belief was that the camphorsulfonic acid was the strongest acid; correct</u>?
R. <u>C'est exact</u>.

(Badorc, cross T4177-4181)

[Emphasis added]

Q. Thank you. We talked about some of the chiral acids yesterday, and I think you mentioned also Jacques and Collet yesterday in your evidence. Am I right that at the time you were going to separate 4099, there was a list of optically active acids that was available, a list of commercial products?

R. Yes. In all the catalogues which can exist, there is – there is a list of chiral – commercially available chiral acids.

Q. Okay. And of that list, would you say perhaps there were about a dozen optically active acids that would have been available to you?

R. At the time, I'd say perhaps even more or even less. I wouldn't know.

Q. Okay.

R. There were chiral acids which were commercially available, which we could see in all of the catalogues, which were available in all labs.

Q. Okay. And would I be correct that of those that were available to you, the strongest at the time that you were doing the separation was camphorsulfonic acid?

R. No.

Q. Do you still have - I told you to put it away, so I'm sorry, but document number 7, the US trial, I would like you to go to page 1817. I would like you to go - do you have it, 1817? I think you have it, because it looks like you are reading. 1817, I would like you to go to line 11. You were asked the question by the Court on that occasion:

> "What is the universe that you start with of optically-active acids? How many are in this list or lists that you are referring to?"

You say at line 14:

> "I would say that perhaps there are about a dozen optically-active acids, and the strongest being - now, I'm talking about the strongest at the time that we were doing this, was camphorsulfonic acid." [As read]

Were you asked that question by the Court and did you give that answer to the Court on February 7th, 2007 in the US trial?

R. That is the question I gave the Court, because I thought I had to put ticlopidine acid in the series of tubes, and it is true that I thought that camphorsulfonic was the strongest. And it is only after I looked at it that I noticed that the tartaric acid, which I thought weaker than camphorsulfonic, was not so. In fact, it was toluoyl tartaric which was the strongest. But at the time when I testified in the United States, I thought that the camphorsulfonic acid, yes, was stronger than the dibenzoyl tartaric acid in a control afterwards, and it was in fact toluoyl (ph.) tartaric acid was the strongest and, after, camphorsulfonic acid.

Q. So after the trial, you learned or discovered that the camphorsulfonic acid was not the strongest acid. You learned that after the trial; correct?

R. After the trial, yes. I know that the other was strong acid, but I thought that camphorsulfonic acid was stronger than the dibenzoyl (inaudible) tartaric acid, and I was surprised but in fact the strongest is the dibenzoyl tartaric acid.

Q. So up until the trial, your belief that the camphorsulfonic acid was the strongest acid, then, because that is the answer you gave to the Court?
R. Yes, I thought so. I thought the camphorsulfonic was stronger.
Q. When you did the separation of 4099, your belief was that the camphorsulfonic acid was the strongest acid; correct?
R. That is correct.

(Badorc, English RD7532)

[Emphasis added]

[780] The Court observes that Mr. Badorc's recollection regarding the solvents used changed and seemed to improve between this case and previous cases. For instance, Mr. Badorc indicated that he used acetone and ethyl alcohol with the acids at trial, whereas he could not provide an answer in this regard in an earlier case (Badorc, T4035).

[781] Also, it is noteworthy that Mr. Badorc decided to conduct his work on PCR 4099 using the asymmetrical synthesis route instead of the diastereomeric salt resolution. This decision stems from the fact that the diastereomeric salt resolution that proved to be successful with PCR 1033 proved to be unsuccessful with PCR 3549. This led Mr. Badorc to take a "detour" and spend time trying to separate PCR 4099 using the asymmetric synthesis technique. This is a detour that the POSITA would not have taken.

[782] When Mr. Badorc eventually reverted to the diastereomeric salt resolution technique, he was successful in separating the enantiomers of PCR 4099. The separation of PCR 1033, PCR 3549 and eventually PCR 4099 can in fact be viewed in a *continuum*. The bulk of the time that Mr. Badorc spent on PCR 4099 seemed to be in respect of his attempted asymmetrical synthesis. Indeed, Mr. Badorc took that avenue of diastereomeric salt resolution in performing the separation on PCR 1033

with no failed steps (Badorc, T4014). As noted, it is the work on PCR 3549 performed by Mr. Badorc that led him to take a "detour" in using the asymmetrical synthesis technique. However after two (2) attempts using the assymetrical synthesis, he eventually reverted to the diastereomeric salt resolution technique he had used in successfully separating PCR 1033 and was in turn successful in separating the enantiomers of PCR 4099. A person of ordinary skill in the art would not be led from the outset to attempt asymmetrical synthesis to obtain the enantiomers of PCR 4099. Hence, on the evidence of this record, the Court finds that the actual course of conduct performed by Mr. Badorc revealed no substantial difficulty.

(5) Conclusion on Obviousness

[783] In sum, the Court finds that the PCR 4099 compound, albeit not its properties, was part of the common general knowledge and was featured in the '875 genius Patent; the POSITA would have been directed towards the classic Pasteur method; the relevant solvants most commonly used in diastereomeric salt resolution (Pasteur method) were known; the selection of salts was a well-known established methodology at the relevant time; there was a motivation to separate the enantiomers of PCR 4099 at the relevant date.

[784] In weighing all of the factors on a balance of probabilities, the Court concludes that the invention in the '777 Patent was "obvious to try" and, therefore, the '777 Patent and its claims are invalid.

IX Overall Conclusions

[785] In conclusion, Apotex' impeachment action in Court File No. T-644-09 is accordingly allowed. As a consequence, Sanofi's action in Court File No. T-933-09 is dismissed.

[786] In summary, the Court has found that each of the claims of the '777 Patent are invalid for lack of utility. More particularly, the Court has found that the '777 Patent does not disclose the requirements for sound prediction.

[787] Further, in the event the '777 Patent disclosed the requirement for sound prediction, the Court has found on the basis of the record before it, and on balance of probabilities, that the claims were obvious as of the appropriate date for obviousness.

[788] With respect to costs, the parties will be given a period of time to attempt to resolve the issue of costs amongst themselves. Prothonotary Tabib has advised the Court that she would be available to assist the parties in settling this matter. The Court has confidence that the parties will succeed.

[789] Should the parties be unable to agree on costs, they may serve and file written submissions as to costs on or before Friday, January 13, 2012. Such submissions should not exceed ten (10) pages. Reply submissions should not exceed five (5) pages and may be served and filed by Friday, January 27, 2012.

[790] Finally, the Court reiterates its thanks to the parties' counsel involved in this litigation for their professionalism, respect and courtesy vis-à-vis each other and vis-à-vis the Court.

POSTCRIPT

[1] These Public Reasons for Judgment are a redacted version of the Confidential Reasons for Judgment which were issued on December 6, 2011 pursuant to the Direction dated December 6, 2011. The parties advised the Court on December 13, 2011 that portions of the Confidential Reasons for Judgment should be redacted.

"Richard Boivin"

Judge

APPENDIX A

List of Witnesses

A. *Apotex' Expert Witnesses*

(1) Dr. Jack Hirsh

Dr. Jack Hirsh is a medical doctor in clinical and research haematologist with particular expertise in anticoagulant, platelet and thrombosis research and therapy and in the diagnosis, prevention and treatment of arterial and venous thrombosis in humans.

Dr. Hirsh gave evidence with regards to Haemostasis and Thrombosis. He gave some background as to how platelets function and how arterial and venous thrombosis is formed. He also gave evidence as to which tests were commonly used to measure platelet aggregation and/or platelet inhibition properties and discussed the ones used in the '777 Patent. Dr. Hirsh also addressed the issue of animal models, species differences and extrapolation from animals to humans. Finally, Dr. Hirsh gave evidence about the PCR 4099 abstracts.

(2) Dr. James E. Sanders

Dr. James Sanders is a toxicologist specialized in veterinary toxicology, toxicological and veterinary pathology, safety, pharmacology, and risk assessment. He has particular expertise in the application of the knowledge from these fields to the design, conduct, assessment and conclusions that may be drawn from animal or human studies as predictors of human toxicological responses in the context of the development of pharmaceuticals for human use, regulatory requirements in

respect of the provision of toxicological information for pharmaceuticals intended for human use and the presentation of toxicological data to the FDA, including IND submissions.

Dr. Sanders gave evidence with regards to toxicology. He provided some background about the principles of ADME, the LD_{50} tests, the ED_{50} tests and the calculation of the therapeutic index. He also addressed the issue of the toxicity studies done for PCR 4099, those for the '875 Patent as well as those in Table IV of the '777 Patent. He also provided evidence on human testing and the extrapolation of toxicity data from rats to humans.

(3) Dr. Irving Wainer

Dr. Irving Wainer is an expert in medicinal chemistry and the stereospecific pharmacology of chiral drugs, including their stereochemical and pharmacological properties, synthesis and resolutions thereof, and their metabolic and pharmacologic behaviour. Dr. Wainer is also an expert in regulatory requirement and practices of pharmaceutical companies regarding racemic drugs and their enantiomers, their development and submissions to regulatory authorities.

Dr. Wainer gave evidence with regards to chemistry and chiral compounds. He provided a background on the history of chiral chromatography (HPLC) and explained the techniques used to separate enantiomers. More particularly, he addressed the issue of the Pirkle column, the ADG column and the Cyclodextrin column. Dr. Wainer explained the difference between chiral medicine and chiral property. He also provided background about the regulatory reasons to separate enantiomers (the 1992 FDA policy).

(4) Dr. Brian M. Adger

Dr. Brian Adger is an expert in pharmaceutical chemistry, including the synthesis of chiral pharmaceutical molecules, the formation of salts of pharmaceutical molecules, the resolution of antimeric pharmaceutical molecules from racemic mixtures, and the direct synthesis of enantiomeric pharmaceutical molecules and the chemical development of new drugs in the pharmaceutical industry, including the development of new chiral drugs and single enantiomer drugs.

Dr. Adger gave evidence on the isolation of single enantiomers. He addressed the issues of diasteriomeric resolution as well as asymmetric synthesis.

(5) Dr. Rene H. Levy

Dr. Rene Levy is an expert in pharmacology with particular expertise in the biopharmaceutics, metabolism, disposition, pharmacokinetics and pharmacodynamics of drug products and their metabolites.

Dr. Levy provided evidence on pharmacodynamics and the kinetics of racemic drugs. He addressed the issues of metabolites (secondary and tertiary) and their roles in the metabolism. More particularly, he addressed the issue of interspecies differences with regards to metabolism. Finally, he gave evidence on double blind human studies.

The Court also recognized that Dr. Levy had experience in chiral molecules including how pharmacological responses in these areas vary in different animal species, including humans.

B. *Apotex' Fact Witnesses*

(1) Donald John Barber

Mr. Donald Barber is currently the Formulation Development New Products Manager at Apotex Inc. Mr. Barber worked for Apotex Inc. in the formulation development group throughout the relevant period.

Mr. Barber gave evidence about the nature of the work entailed in developing dosage formulations, including the nature of the work involved in first evaluating and determining the relevant physico-chemical characteristics of the active ingredient, and the various steps involved in the pre-formulation and formulation development process, and the preparation and evaluation of those batches of the final dosage form submitted for approval to regulatory authorities.

(2) Galina Ayyoubi

Ms. Galina Ayyoubi is the Quality Assurance Manager of process manufacturing at Apotex Inc. Ms. Ayyoubi is responsible for developing and implementing the quality control protocols and procedures governing the use and handling of material involved in the preparation of pharmaceutical products.

Ms. Ayyoubi gave evidence about the nature of Apotex' quality control procedures and protocols, and their implementation with respect to the receipt and use of clopidogrel and clopidogrel salts.

(3) John Hems

Mr. John Hems was formerly the Director of Regulatory Intelligence at Apotex Inc. Mr. Hems was employed by Apotex Inc. in the regulatory affairs group throughout the relevant period.

Mr. Hems gave evidence regarding the development of the Apo-clopidogrel regulatory submissions. He identified the information required to be contained in regulatory submissions, including those relating to clopidogrel. He also gave evidence concerning the characteristics and properties of the active ingredient used in dosage formulations, and the dosage formulations themselves, and identified those extracts from Apotex' regulatory submissions that related to Apotex' use of clopidogrel for these purposes. He also gave evidence regarding the limitations issue.

(4) Jose Miguel Lazcano Seres

Mr. Miguel Lazcano Seres is the Technical Director of […] .

Mr. Seres gave evidence about the method used to manufacture the clopidogrel sold to Apotex.

(5) Edson Sanchez

Mr. Edson Sanchez is the Plant Manager of […] .

Mr. Sanchez gave evidence about the method used to manufacture the clopidogrel sold to Apotex.

(6) Antoniette Walkom

Ms. Antoniette Walkom is the Vice-President of the Quality Assurance and Regulatory Affairs, Apotex Pharmachem. Ms. Walkom gave evidence about Apotex Pharmachem's operations generally and, in particular, its research and development activities with respect to clopidogrel, including its regulatory filings.

(7) Dr. Bernard Sherman

Dr. Bernard Sherman is the Chair of Apotex Inc.

Dr. Sherman gave evidence about the corporate organization and history of the Apotex companies, the supply of active pharmaceutical ingredients, including clopidogrel and the development of Apo-clopidogrel.

Dr. Sherman also explained the Canadian litigation relating to Apo-clopidogrel, the sale of Apo-clopidogrel, including the terms of trade relating to same, the U.S. litigation relating to Apo-clopidogrel, the circumstances surrounding entry into the March and May 2006 Settlement Agreements, the limitations issue and the issue of experimental use.

(8) Dr. Robert W. Colman

Dr. Robert Colman is a professor emeritus at Temple University.

Dr. Colman described what occurred at the Xth International Congress on Thrombosis and Haemostasis and the Joint Congress of the International Society of Thrombosis and Haemostasis.

He also described his knowledge of the abstracts and posters presented at these conferences and their publication.

(9) Gordon Eli Fahner

Mr. Gordon Fahner is currently the Vice President of Supply Chain at Apotex Inc. Mr. Fahner has been employed at Apotex in progressively senior positions in the accounting area.

Mr. Fahner was thoroughly familiar with the internal systems and procedures used at Apotex to record and track the receipt and subsequent use of the materials used in developing dosage formulations and implementing Apotex' manufacturing processes.

Mr. Fahner gave evidence relating to the quantities of clopidogrel that were used by Apotex for all experimental and regulatory purposes, and how those quantities were calculated.

Mr. Fahner also addressed the corporate organization of the Apotex companies, the supply of active pharmaceutical ingredients, including clopidogrel, the supply and usage of excipients, including those related to Apo-clopidogrel, the development of Apo-clopidogrel. He also explained the sale of Apo-clopidogrel, including the terms of trade relating to same, the U.S. litigation relating to Apo-clopidogrel, the limitations issue and the issue of experimental use.

C. *Sanofi's Expert Witnesses*

(1) Dr. Stephen R. Byrn

Dr. Stephen Byrn has expertise in medicinal, organic and solid state chemistry with experience in stereochemistry and chiral compounds, with experience in the use and characterization of pharmaceutical salts which include formulation of drug products, including the advantage of avoiding hygroscopicity, water solubility and crystallinity, and some experience in the accessibility of scientific literature in the mid to late 1980s.

Dr. Byrn provided evidence on the different methods to separate enantiomers. Regarding separation, he responded to Dr. Wainer's evidence. Dr. Byrn addressed the issue of salts. More particularly, he discussed the lists of salts, the properties of salts and the screening of salts. He also provided evidence to compare Apotex' process to make clopidogrel with Sanofi's process (Claim 6 of the '777 Patent).

(2) Dr. Joseph V. Rodricks

Dr. Joseph Rodricks is a toxicologist with experience in the use of toxicological data in safety and risk assessment, the ability to extrapolate from animal data, and experience with regulatory and drug approval process.

Dr. Rodricks provided evidence with regards to toxicology. He responded to Dr. Sanders' evidence. Dr. Rodricks discussed pre-clinical testing as well as adverse effects of drugs. He also discussed Sanofi's internal studies on toxicology for the '777 Patent.

(3) Dr. Stephen G. Davies

Dr. Stephen Davies is an expert in medicine and organic chemistry medicinal and organic chemist, with experience in stereochemistry and chiral compounds, the methodologies used to obtain individual enantiomers, the biological impact of chiral differences. He also has experience in the accessibility of scientific literature in the mid to late 1980s and some experience with whether there were regulatory policies in the late 1980s with respect to drugs that have a chiral centre.

Dr. Davies gave evidence with regards to the separation of enantiomers. More particularly, he held that it was not an easy task and that it had to be done "from scratch". He gave evidence about the motivation to separate and a brief background as to the growing interest in enantiomers. He also provided evidence about PCR 4099. Finally, he discussed the properties of compounds and the importance of their quantity.

(4) Dr. Ronald J. Shebuski, SR

Dr. Ronald Shebuski is qualified as a cardiovascular pharmacologist with experience in hemostasis and thrombosis, the pharmacology and development of antithrombotic and antiplatelet agents, *in vivo*, *in vitro*, and *ex vivo* techniques used to assess the biological activity of antiplatelet and antithrombotic agents, the ability to extrapolate based on the results from these techniques and some experience in the accessibility of scientific literature in the mid to late 1980's.

Dr. Shebuski gave evidence on haematology. He responded to Dr. Hirsh's evidence. More particularly, he discussed the issues of metabolites and human extrapolation. He addressed the issue

of the metabolites and their role in this instance. Finally, he gave his opinion on the sound prediction of the ‘777 Patent.

D. *Sanofi’s Fact Witnesses*

(1) Dr. Thierry Saugier

Dr. Thierry Saugier is the Vice-President, Alliance and Partnership at Sanofi-Aventis.

Dr. Saugier described the organization of the plaintiff, Bristol-Myers Squibb, Sanofi Pharmaceuticals Holding Partnership (the “Partnership”) and its role in the marketing of Plavix® (clopidogrel bisulfate). Dr. Saugier also discussed agreements relating to the licensing of intellectual property rights, including Canadian Patent 1,336,777, by Sanofi-Aventis to the Partnership.

(2) Dr. Judith Lynn Weissinger

Dr. Judith Weissinger is the President and CEO of Weissinger Solutions Inc.

Dr. Weissinger gave evidence concerning the approach adopted by the U.S. Food & Drug Administration (FDA) to the approval of racemates in the mid-1980s to the early 1990s. Dr. Weissinger also gave evidence on her experiences as Chair of the Center for Drug Evaluation and Research Stereoisomers Committee.

(3) Dr. Frédéric Lacheretz

Dr. Frédéric Lacheretz is a toxicologist and doctor in Veterinary Medicine. He joined Sanofi-Aventis (or its predecessors) in around 1983 and remained at Sanofi-Aventis for over twenty years. As Head of Toxicological Laboratory Studies at the relevant time, Dr. Lacheretz was involved in and supervised toxicological studies in respect of thienopyridine compounds, in particular PCR 4099 and clopidogrel, conducted in the 1980s by Sanofi-Aventis.

(4) Mr. Alain Badorc

Mr. Alain Badorc is a retired chemist at Sanofi-Aventis. He is one of the named inventors of Canadian Patent No. 1,336,777 (the '777 Patent). Prior to his retirement, Mr. Badorc was the laboratory executive of the laboratory in the Thrombosis and Angiogenesis Department of Sanofi-Aventis, Toulouse, France. He provided evidence of his work on thienopyridines.

(5) Dr. Jean-Pierre Maffrand

Dr. Jean-Pierre Maffrand is a retired scientist and former senior executive at Sanofi-Aventis. He supervised the inventors of Canadian Patent No. 1,336,777 ('777 Patent), Mr. Alain Badorc and Dr. Daniel Fréhel. Prior to retirement, Dr. Maffrand was the Senior Vice-President, Director of Discovery Research at Sanofi-Aventis, Toulouse, France.

Dr. Maffrand gave evidence on the research he conducted and/or supervised on thienopyridines and in particular the following compounds: PCR 1033, PCR 3549, PCR 4099, clopidogrel, levo-rotatory enantiomer, '875 compounds. Dr. Maffrand also gave evidence about the development of PCR 4099, the separation of PCR 4099 into its enantiomers, the activity tests

performed on clopidogrel, the levo-rotatory enantiomer and PCR 4099, the decision to discontinue the development of PCR 4099 and the results of the clopidogrel Phase I clinical trials in healthy human volunteers.

APPENDIX B

EXHIBIT 22

STUDY		SPECIES	PCR 4099	CLOPIDOGREL
***Ex vivo* platelet aggregation study**	**ADP**	**Rat**	Single oral administration study ♀; dose tested (mg/kg): 25; performed assays at regular intervals over 48h period after treatment • Report: SA241	Single oral administration study ♀; doses tested (mg/kg): 2.5 & 10; performed assays at regular intervals over 72 h period after treatment • Report: SA414 (p. 8) • Lab notebook: SA111 (pp. S05135-S05148)
				Single oral administration study ♀; doses tested (mg/kg): 2.5, 10; performed assays at regular intervals over 6h period after treatment • Report: SA414 (p. 17) • Lab notebook: SA111 (p. S05135-S05141)
			Single oral administration studies ♀, doses tested (mg/kg): various between 2.5-17.9; performed assay 2h after treatment • '777 patent (SA1) • Reports: SA324, SA331 (pp. S276403-S276404), SA353, SA363, SA389, SA390	Single oral administration studies ♀, doses tested (mg/kg): various between 1.25-25; performed assay 2h after treatment • '777 patent (SA1) • Lab notebook: SA94 (pp. S16214-S16218), SA109 (pp. S13796-S13798) • Reports: SA324, SA331 (pp. 276403-S276404), SA353, SA363, SA389, SA390 • See also: lab notebook SA111 (pp. S05085-S05088)

STUDY		SPECIES	PCR 4099	CLOPIDOGREL
			Single oral administration study ♀ & ♂; dose tested (mg/kg): 25; performed assay 2 hours after treatment • Lab notebook: SA94 (pp. S16208-S16213)	Single oral administration studies; doses tested ♀ (mg/kg): 1.25, 2.5, 5, 10; doses tested ♂ (mg/kg): 2.5, 5, 10, 20; performed assay 2h after treatment • Report: SA414 (p. 10) • Lab notebooks: SA110 (pp. S05035-S05052), SA111 (pp. S05089-S05095)
			Repeated oral administration studies over 3 days; doses tested (mg/kg/day): various between 1-25 • '875 patent • Reports: SA305 (pp. S65205-S65206), SA340 (p. S09782)	Repeated oral administration study over 3 days; doses tested ♀ (mg/kg/day): 0.625, 1.25, 2.5, 5; doses tested ♂ (mg/kg): 1.25, 2.5, 5, 10 • Report: SA414 (pp. 22-23) • Lab notebook: SA111 (pp. S05108-S05117)
				Repeated oral administration study over 5 days ♀, dose tested (mg/kg/day): 2.5 • Lab notebook: SA131 (pp. S05205-S05208)
		Baboon	Repeated oral administration studies ♀ & ♂ over 6 days; doses tested (mg/kg/day): various between 3.7- 30 • Abstract (SA457) • Investigational brochures: SA340 (p. S09872), SA305 (pp. S65206-S65207)	Repeated oral administration study over 7 days; doses tested (mg/kg/day): 25, 100, 400 • Report: SA397

STUDY		SPECIES	PCR 4099	CLOPIDOGREL
	Collagen	Rat	Single oral administration study ♀; dose tested (mg/kg): 25; performed assays at regular intervals over 48h period after treatment • Report: SA241	Single oral administration study ♀; doses tested (mg/kg): 2.5 & 10; performed assays at regular intervals over 72 h after treatment: • Report: SA414 (p. 9) • Lab notebook: SA111 (pp. S05135-S05148)
				Single oral administration study ♀; doses tested (mg/kg): 2.5, 10; performed assays at regular intervals over 6h period after treatment: • Report: SA414 (p. 17) • Lab notebook: SA111 (pp. S05135-S05141)
			Single oral administration studies ♀, doses tested (mg/kg): various between 2.5-17.9; performed assay 2h after treatment • '777 patent (SA1) • Reports: SA324, SA331 (pp. S276403-S276404), SA353, SA363, SA389, SA390	Single oral administration studies ♀, doses tested (mg/kg): various between 1.25-25; performed assay 2h after treatment • '777 patent (SA1) • Lab notebook: SA94 (pp. S16214-S16218) • Reports: SA324, SA331 (pp. 276403-S276404), SA353, SA363, SA389, SA390 • See also: lab notebook SA111 (pp. S05085-S05088)

STUDY		SPECIES	PCR 4099	CLOPIDOGREL
			Single oral administration study ♀ & ♂; dose tested (mg/kg): 25; performed assay 2 hours after treatment • Lab notebook: SA94 (pp. S16208-S16213)	Single oral administration studies; doses tested ♀ (mg/kg): 1.25, 2.5, 5, 10; doses tested ♂ (mg/kg): 2.5, 5, 10, 20; performed assay 2 hours after treatment: • '777 patent (SA1) • Reports: SA414 (p. 11) • Lab notebooks: SA110 (pp. S05035-S05052), SA111 (pp. S05089-S05095)
			Repeated oral administration studies over 3 days; doses tested (mg/kg/day): various between 1-25 • '875 patent • Reports: SA305 (pp. S65205-S65206), SA340 (p. S09782)	Repeated oral administration studies over 3 days; doses tested ♀ (mg/kg/day): 0.625, 1.25, 2.5, 5; doses tested ♂ (mg/kg/day): 1.25, 2.5, 5, 10: • Report: SA414 (pp. 24-25) • Lab notebook: SA111 (pp. S05108-S05121)
				Repeated oral administration study over 5 days ♀, dose tested (mg/kg/day): 2.5 • Lab notebook: SA131 (pp. S05205-S05208)
	Thrombin	**Rat**	Single oral administration study ♀; doses tested (mg/kg): 5, 12.5, 15; performed assay 2 hours after treatment: • Report: SA449 (pp. SR78584-SR78585)	Single oral administration studies; doses tested ♂ (mg/kg): 2.5, 5, 10, 20; doses tested ♀ (mg/kg): 1.25, 2.5, 5, 10; performed assay 2 hours after treatment: • Reports: SA414 (p. 12) • Lab notebook: SA111 (pp. S05098-S05107)

STUDY	SPECIES	PCR 4099	CLOPIDOGREL
		Repeated oral administration studies over 3 days ♀; doses tested (mg/kg/day): 1, 2.5, 5 • Abstract (SA457) • Investigational brochures: SA340 (p. S09782), SA305 (pp. S65205-S65206)	Repeated oral administration studies over 3 days; doses tested ♀ (mg/kg/day): 0.625, 1.25, 2.5, 5; doses tested ♂ (mg/kg/day): 1.25, 2.5, 5, 10: • Report: SA414 (pp. 26-27) • Lab notebook: SA131 (pp. S05221-S05228)
Arterio-venous shunt (extracorporeal) model	**Rat**	Single oral administration studies ♀; doses tested (mg/kg): 10, 12.5, 25 • Lab notebook: SA50 (pp. S05715-S05716, S05719-S05720)	Single oral administration study ♀; doses tested (mg/kg): 1.25, 2.5, 5, 10, 20 • Report: SA414 (p. 48) • Lab notebook: SA113 (pp. S05197-S05199)
		Single oral administration studies ♂; doses tested (mg/kg): various between 8.97-35.9 • Lab notebooks: SA50 (pp. S05717-S05718), SA113 (pp. S05194-S05195)	Single oral administration study ♂; doses tested (mg/kg): 5, 10, 20 • Lab notebook: SA113 (pp. S05194-S05195)
		See also: • '875 patent • Reports: SA305 (pp. S65209-S65211), SA340 (p. S09784)	

STUDY	SPECIES	PCR 4099	CLOPIDOGREL
Metallic coil thrombosis model	**Rat**	Single oral administration studies ♀; doses tested (mg/kg): various between 4.48-50 • '777 patent (SA1) • Reports: SA389, SA390 • Lab notebooks: SA90 (pp, S05609-S05610, S05615-S05616, S05629-S05630, S05638-S05642), SA 49 (p. S05690)	Single oral administration studies ♀; doses tested (mg/kg): various between 1.25-20 • '777 patent (SA1) • Reports: SA414 (p. 51), SA389, SA390 • Lab notebook: SA90 (pp. S05638-S05642, S05647-S05648, S05651-S05652, S05653-S05654)
		Single oral administration studies ♂; doses tested (mg/kg): various between 8.97-35.9 • Reports: SA313, SA331 (pp. S276403, S276405), SA353, SA363 • Lab notebook: SA90 (pp. S05643-S05644)	Single oral administration studies ♂; doses tested (mg/kg): various between 2.5-25 • Reports: SA313, SA331 (pp. S276403, S276405), SA353, SA363 • Lab notebook: SA90 (pp. S05643-S05644)
		See also: • Reports: SA305 (pp. S65209-S65211), SA340 (p. S09784) • Lab notebooks: SA72 (p. S16656), SA114 (p. S59049)	See also: • Lab notebooks: SA72 (pp. S16649-S16655), SA90 (pp. S05623-S05624)
Venous stasis model	**Rat**	Single oral administration studies ♀; doses tested (mg/kg): various between 4.46-53.8 • Lab notebook: SA89 (pp. S05556-S05557-S05561, S05567)	Single oral administration studies ♀; doses tested (mg/kg): 1.25, 2.5, 5, 10, 20, 30: • Report: SA414 (pp. 54-55) • Lab notebook: SA89 (pp. S05567-S05575)

STUDY	SPECIES	PCR 4099	CLOPIDOGREL
		See also: • Reports: SA305 (pp. S65209-S65211), SA340 (p. S09784)	
Bleeding time study	**Rat**	Single oral administration studies ♀; doses tested (mg/kg): various between 2.5-25 • Lab notebook: SA73/112 (pp. S05502-S05504, S05507-S05508, S05510-S05511, S05518-S05519)	Single oral administration studies ♀; doses tested (mg/kg): 1.25, 2.5, 5, 10, 20 • Lab notebook: SA73/112 (pp. S05522-S05523)
		Single oral administration study ♂; dose tested (mg/kg): 25 • Report: SA245 • Lab notebook: SA73/112 (pp. S05520-S05521)	Single oral administration study ♂; dose tested (mg/kg): 2.5 • Lab notebook: SA73/112 (pp. S05526-S05527)
		See also: • Reports: SA305 (pp. S65208-S65209), SA340 (p. S09783)	
Platelet adenylate cyclase activity	**Rat**	n/a	Single oral administration study; dose tested (mg/kg): 25 • Report: SA414 (pp. SR78476-SR78477)
	Rabbit	n/a	Repeated oral administration study over 5 days dose tested (mg/kg/day): 50 • Report: SA414 (pp. SR78478-SR78479)

APPENDIX C

DATE	EVENT
1972	Ticlopidine synthesized
1975	PCR 1033 synthesized
1978	Ticlopidine arrived on the French market
June 16, 1977	Resolution of enantiomers of PCR 1033 – PRC 3071, PCR 3072
September 1978	PCR 3071 and PCR 3072 tested for activity and toxicity
November 1978	PCR 3233 synthesized
March 1979	PCR 3549 synthesized
March 1979	Successful resolution of PCR 3549 intermediates to be used in asymmetric synthesis
April 1979	Enantiomers of PCR 3233 (3549) obtained - PCR 3620, PCR 3621
May 1979	PCR 3620 and PCR 3621 tested for activity and toxicity
July 1980	PCR 4099 synthesized
March 1983 – April 1987	Baboon convulsions reported for PCR 4099 (12-month toxicity study)
July 8, 1983	Filing date ‘875 Patent application
End of 1983 – April 1987	PCR 4099, Studies in humans
1985	Japanese guideline re separation of enantiomers
July 14-19, 1985	San Diego conference and Sanofi abstracts and posters
November 1985	Maffrand decision to obtain enantiomers of PCR 4099
March 21, 1986	Badorc obtains l enantiomer of PRC 4099
April 7, 1986	Hydrochloride salt of the L enantiomer made
April 8, 1986	Badorc obtains D enantiomer of PRC 4099
April 15, 1986	Hydrochloride salt of the D enantiomer made
June 1-6, 1986	Jerusalem conference and Sanofi abstracts and posters
September 29, 1986	Vallee memorandum to LeFur *et al.* re “Enantiomers of PCR 4099”, referencing “B-Health Authorities” and Japanese joint venture request for “separation and study of enantiomers”

DATE	EVENT
March 19, 1986	Kumkumian address to the APA
January 1987	Investigator's Brochure indicated that PCR 4099 was highly potent and well tolerated with a very good safety margin
February 1987	FDA guidance policy re "Guidelines for submitting supporting Documentation in Drug Applications For the Manufacture of Drug Substances"
February 17, 1987	First French priority application for '777 Patent
March 31, 1987	Maffrand memorandum to LeFur and Simon re "My perception of PCR 4099 today" referencing "Health authorities" and Japanese joint venture
April 16, 1987	Simon memorandum re "Development PCR 4099" referencing decision to stop development of PCR 4099
May 12, 1987	SR 25990C, bisulfate (hemisulfate) salt prepared
May 18, 1987	Report on toxicity testing on PCR 4099 and hydrochloride salts of 25990 and 25989.
May 20, 1987	SR 25990D, hydrobromide salt prepared
June, 1987	Study Report: Research on Stable Crystalline Salts of SR 25990
September 14, 1987	Report on toxicity testing of salts of SR 25990
November 6, 1987	SR 25990E, taurocholate salt prepared
November 27, 1987	Second French priority application for '777 Patent
December 1987	Start of trial of D enantiomer in humans, ending March 1988
February 8, 1988	Filing date of '777 Patent application

FEDERAL COURT

SOLICITORS OF RECORD

DOCKET:	T-644-09
STYLE OF CAUSE:	Apotex Inc. v. Sanofi-Aventis
DOCKET:	T-933-09
STYLE OF CAUSE:	Sanofi-Aventis and Bristol-Myers Squibb Sanofi Pharmaceuticals Holdings Partnership v. Apotex Inc., Apotex Pharmachem Inc. and Signa Sa de CV
PLACES OF HEARINGS:	Toronto, Ontario Ottawa, Ontario
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APPEARANCES:

Harry Radomski Richard Naiberg Andrew Brodkin Nando De Luca Benjamin Hackett David Scrimger Sandon Shogilev Belle Van	FOR THE PLAINTIFF APOTEX INC.
Anthony G. Creber Cristin A. Wagner Marc Richard Rick Dearden Isabel Rassch Livia Aumand	FOR THE DEFENDANTS SANOFI-AVENTIS

SOLICITORS OF RECORD:

Goodmans LLP Toronto, Ontario	FOR THE PLAINTIFF
Gowling Lafleur Henderson LLP Ottawa, Ontario	FOR THE DEFENDANTS