Federal Court  Cour fédérale

Date: 20180713

Docket: T-1734-16

Citation: 2018 FC 736

Ottawa, Ontario, July 13, 2018

PRESENT: The Honourable Mr. Justice Manson

BETWEEN:

ELI LILLY CANADA INC.,
UBE INDUSTRIES, LTD. AND
DAIICHI SANKYO COMPANY, LIMITED

Applicants

and

APOTEX INC. AND
THE MINISTER OF HEALTH

Respondents

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I. Pleadings

[1] The Applicants are Eli Lilly Canada Inc. ("Eli Lilly"), Ube Industries Ltd. ("Ube Industries") and Daiichi Sankyo Company Ltd. ("Daiichi"). Eli Lilly is a pharmaceutical manufacturer that distributes and sells, among other things, the pharmaceutical EFFIENT® (prasugrel hydrochloride). Ube Industries and Daiichi are the owners of Canadian Patent No. 2,432,644 (the "'644 Patent"). The '644 Patent is listed by Eli Lilly in respect of EFFIENT® on the Patent Registrar maintained by the Minister of Health (the "Minister") pursuant to the *PM(NOC) Regulations*, SOR/93-133 [*PM(NOC) Regulations*].

[2] The Respondent Apotex Inc. (“Apotex”) is a generic pharmaceutical manufacturer. On August 18, 2016, Apotex filed an abbreviated new drug submission (“ANDS”) with the Minister seeking a notice of compliance (“NOC”) for apo-prasugrel, using EFFIENT® as the Canadian reference product. On August 30, 2016, Apotex served a notice of allegation (“NOA”) in which it alleged that the ‘644 Patent is invalid and not infringed by apo-prasugrel.

[3] The Applicants responded to the NOA by commencing this application on October 14, 2016, pursuant to section 6 of the *PM(NOC) Regulations*, seeking an order that it is not a proper NOA and detailed statement for the purposes of the *PM(NOC) Regulations*, or in the alternative, an order prohibiting the Minister from issuing a NOC to Apotex for apo-prasugrel until after the expiry of the ‘644 Patent.

II. Issues

[4] Apotex’s allegations in its NOA are as follows:

1. claims 1-58 of the ‘644 Patent fail to contain a claim for the medicinal ingredient, the formulation, the dosage form or the use of the medicinal ingredient that was approved through the issuance of the NOC;
2. Apotex will not infringe any of the claims of the ‘644 Patent by the making, constructing, using or selling of apo-prasugrel in Canada; and
3. the ‘644 Patent is invalid because:
    a) each of the claims defines subject matter that would have been obvious to a skilled person;

b) utility had not been demonstrated prior to the filing date and the inventors did not comply with the doctrine of sound prediction;

c) the claims are broader than any invention made or disclosed;

d) it does not make a correct and full disclosure;

e) claims 11 (and dependent claims 12-16), 18, 19, 23 (and dependent claims 24-28), 41 (and dependent claims 44-49) and 50 (and dependent claims 53-58) are ambiguous; and

f) the claims are for a mere aggregate and not a patentable combination.

[5] In their written submissions and at the hearing, the parties narrowed the claims at issue to two claims (the "Asserted Claims"):

- claim 22, as it depends from claims 20 and 18 (the use of prasugrel in the preparation of a medicament for simultaneous administration with aspirin, in separate dosage forms, for the prevention or treatment of a disease caused by thrombus or embolus); and
- claim 29 (prasugrel for use in combination with aspirin in preventing or treating a disease caused by thrombus or embolus, administered simultaneously or sequentially).

[6] As well, the issues were narrowed to the following validity attacks:

1. the claims of the '644 Patent do not relate to patentable subject matter;
2. the Asserted Claims are invalid for obviousness;
3. the '644 Patent does not make a correct and full disclosure; and
4. claim 29 is overbroad.

III. Results

[7] The Court's finding on the four issues is as follows:

1. the claims of the '644 Patent do relate to patentable subject matter;
2. the Asserted Claims are invalid for obviousness;
3. the '644 Patent makes a correct and full disclosure; and
4. claim 29 is not overbroad.

IV. Background

A. *The Patent*

[8] The '644 Patent is entitled "Pharmaceutical Composition Comprising Aspirin™ and CS-747", has an international filing date of December 20, 2001, a publication date of July 4, 2002, and was issued on July 23, 2013. It has a Japanese priority date of December 25, 2000, and its national entry into Canada was on June 19, 2003.

[9] The '644 Patent relates to pharmaceutical compositions comprising 2-acetoxy-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine ("prasugrel") or a pharmaceutically acceptable salt thereof, and aspirin, as active ingredients, which possess inhibitory activity against platelet aggregation and thrombogenesis and are useful for preventing or treating diseases caused by thrombus or embolus.

[10] More specifically, the section of the ‘644 Patent entitled “Technical Field” states that the invention relates to: pharmaceutical compositions containing prasugrel and aspirin as active ingredients for prevention or treatment of diseases caused by thrombus or embolus; the use of pharmaceutical compositions comprising prasugrel and aspirin for the manufacture of pharmaceutical compositions for prevention or treatment of diseases caused by thrombus or embolus; and methods for the prevention or treatment of diseases caused by thrombus or embolus by administration of an effective amount of prasugrel and aspirin to warm-blooded animals (particularly humans).

[11] At page 1 of the ‘644 Patent, under “Background Art”, it explains that prasugrel is a known compound that has been described in a previous Japanese patent application and possesses potent inhibitory activity against platelet aggregation. Furthermore, aspirin is a well-known compound that is known to have an inhibiting activity against platelet aggregation. However, pharmaceutical compositions containing both compounds have not been known.

[12] At pages 3b and following of the ‘644 Patent, under “Industrial Applicability”, it states that the use of prasugrel and aspirin in combination results in more potent effectiveness than the use of each component alone. Furthermore, plasma levels of these two agents do not have to be maintained at a certain level and higher during the same period in order to produce their effects; therefore, they can be administered separately and sequentially.

[13] Asserted Claims claim 22 (as it depends from claims 20 and 18) and claim 29 provide:

> 18. Use of [prasugrel] or a pharmaceutically acceptable salt thereof in the preparation of a medicament for simultaneous or sequential administration with aspirin, for the prevention or treatment of a disease caused by thrombus or embolus.
>
> 20. A use according to claim 18 or 19, where the medicament is for simultaneous administration.
>
> 22. A use according to claim 20, wherein the simultaneous administration is by separate administration of said aspirin and said [prasugrel] or a pharmaceutically acceptable salt thereof.
>
> 29. A compound which is [prasugrel], or a pharmaceutically acceptable salt thereof, for use in combination with aspirin in preventing or treating a disease caused by thrombus or embolus.

V. Applicants' Fact Witnesses

A. *Dr. Atsuhiro Sugidachi*

[14] Dr. Sugidachi is a named inventor on the '644 Patent and currently a senior director/chief scientist at Daiichi. He obtained a degree in pharmaceutical sciences in 1987, a master's degree in 1989 and a PhD in pharmaceutical sciences in 1996. He joined Sankyo Company Ltd. ("Sankyo"), a precursor to Daiichi, in 1989 to work in their biological research laboratories as a member of the thrombosis drug development research group (the "Thrombosis Group").

[15] Dr. Sugidachi was asked to describe his work at Sankyo that led to the subject matter of the '644 Patent, in particular, his research on any prasugrel and aspirin combinations that were conducted before December 20, 2001, the filing date of the '644 Patent.

[16] He stated that his first project involved trying to find a new ADP-receptor antagonist compound with antiplatelet activity that could be developed into a drug for clinical use. The Thrombosis Group sought a compound with an improved profile (stronger antiplatelet activity and fewer side effects) compared to ticlopidine, which was an antiplatelet drug that was approved for sale in Japan at that time. Sankyo collaborated with Ube Industries to synthesize hundreds of compounds, including prasugrel.

[17] Dr. Sugidachi explained that by the early 1990s, prasugrel had been selected as a candidate for development as an antiplatelet drug. Many studies on prasugrel were conducted and published during the mid to late-1990s. It was found to be a potent antiplatelet/antithrombotic agent – more potent than ticlopidine in various experimental animals with minimum activity in general toxicological studies. It was well-tolerated by humans in clinical trials.

[18] In or around 1996, Dr. Sugidachi started investigating the effects of prasugrel in combination with aspirin. Four internal Sankyo reports that relate to those studies were attached to his affidavit.

[19] The first report, [redacted] ("Sankyo Report 1"), contained results from an *ex vivo* platelet aggregation study on the combination of prasugrel and aspirin in rats. Dr. Sugidachi helped to design this study and was responsible for conducting the experiments. The report stated that prasugrel in combination with aspirin showed [redacted]

[redacted]

[20] The second report, [redacted] ("Sankyo Report 2") described the antithrombotic effect of prasugrel in combination with aspirin in rats, as well as the effect of the combination of prasugrel and aspirin on bleeding time in rats. Dr. Sugidachi wrote this report and was responsible for performing the work with a lab technician. Antithrombotic effects were studied using an arterio-venous shunt ("AV-shunt") model of thrombosis. He stated that the combination of prasugrel and aspirin resulted in a [redacted] Table 1 on page 8 of the '644 Patent contains some of the data that were produced in this study.

[21] Dr. Sugidachi noted other internal Sankyo reports involving aspirin-prasugrel combination studies. One report, [redacted] ("Sankyo Report 3"), confirmed [redacted] in beagle dogs. Another report, [redacted] ("Sankyo Report 4") compared the antiplatelet effects of aspirin with prasugrel versus aspirin with clopidogrel in rats, and showed [redacted]

[22] He explained that prior to these studies, it was uncertain if there would be a benefit to using prasugrel and aspirin together. He was concerned the combination would cause too much bleeding. [redacted]

[redacted] Based on the data, he concluded that there would be a benefit to using a combination of prasugrel and aspirin in humans for the treatment or prevention of diseases caused by thrombus or embolus.

B. *Dr. Taketoshi Ogawa*

[23] Dr. Ogawa is a named inventor on the ‘644 Patent and a senior director at Daiichi. He has a Master’s degree in pharmacy and obtained a PhD in pharmaceutical sciences in 2001. He joined Daiichi (then Sankyo) in 1993 to work with the Thrombosis Group. At that time, he reported directly to Dr. Sugidachi.

[24] Dr. Ogawa was asked to describe his research on any prasugrel and aspirin combination studies performed before December 20, 2001. His affidavit contains the same four Sankyo Reports that were discussed by Dr. Sugidachi.

[25] Sankyo Report 3, of which he was the author, described research on the effects of prasugrel, aspirin and their combination on platelet aggregation in dogs. He concluded in that report that the combined use of prasugrel and aspirin showed [redacted]

[26] Sankyo Report 4 described a study that Dr. Ogawa was involved in, which compared the combined *ex vivo* antiplatelet effect of prasugrel and aspirin in rats, to that of clopidogrel and

aspirin, 30 minutes after oral administration. The author of that report concluded that the combination of prasugrel and aspirin, [redacted]

[27] The other two reports also involved studies on the combination of prasugrel and aspirin, and were conducted before the ‘644 Patent was filed (Sankyo Reports 1 and 2).

[28] Based on all of these reports, Dr. Ogawa believed that aspirin and prasugrel in combination would be a useful antithrombotic therapy in animals and humans.

C. *Ms. Mary Mutchler*

[29] Ms. Mutchler is a law clerk at Belmore Neidrauer LLP. Her affidavit attaches a certified copy of the ‘644 Patent, the Apotex NOA and documents cited therein, extracts from the Apotex ANDS, and court filings and orders relating to this proceeding.

VI. Applicants’ Expert Witness

A. *Dr. Robert Falotico*

[30] Dr. Falotico is currently a private consultant to the medical device and pharmaceutical industry. He obtained a Bachelor’s degree in Biomedical Sciences in 1974 from Brown University in Providence, Rhode Island and a PhD in Pharmacology in 1980 from the University of Minnesota, School of Medicine.

[31] In 2013, Dr. Falotico retired from Johnson & Johnson, where he had been engaged in pharmaceutical and medical device research and development for 34 years. He began working at Johnson & Johnson in 1980 in Cardiovascular Drug Discovery. From 1991 to 1995, he was the Assistant Director of Drug Discovery Research, the Head of Cardiovascular Pharmacology and Co-leader of the Thrombosis Research Team. After 1995, he continued to be involved with the Thrombosis Research Team, but was also focused on finding new treatments for stent-related thrombosis and restenosis (major complications of stent placement) and led a research team that developed the first drug-eluting stent for the treatment of restenosis.

[32] Dr. Falotico has extensive expertise in the field of cardiovascular pharmacology and drug discovery, including developing treatments for cardiovascular diseases. He has authored approximately 45 peer-reviewed publications, over 90 published abstracts and is an inventor or co-inventor on 27 issued US patents. He received numerous awards and honours throughout his career at Johnson & Johnson.

[33] Dr. Falotico submitted an expert report on issues directly related to validity and infringement of the ‘644 Patent. Portions of his submissions are provided throughout these reasons where they are relevant to the Court’s analysis.

VII. Respondents' Fact Witness

A. *Ms. Lisa Ebdon*

[34] Ms. Ebdon is a law clerk at Goodmans LLP. Her affidavit attaches copies of certain documents listed in Schedule B of the NOA.

VIII. Respondents' Expert Witnesses

A. *Dr. Randall Zusman*

[35] Dr. Zusman is an Associate Professor in Medicine at Harvard Medical School and a physician at Massachusetts General Hospital ("MGH") in Boston, Massachusetts. He obtained a BSc in chemistry from the University of Michigan in 1969 and a MD from the Yale University School of Medicine in 1973.

[36] Dr. Zusman is a practicing physician with over 44 years of experience in medicine generally, and over 42 years in cardiology, both as a physician and clinical researcher. He has held major administrative positions as a Director at the MGH Cardiac Unit and at the Cardiac Rehabilitation Program at Spaulding Rehabilitation Hospital in Boston, Massachusetts. Since 1982, he has been the Director of the Hypertension Section, Cardiac Division, MGH Medical Services.

[37] Dr. Zusman became an Associate Professor in Medicine at Harvard Medical School in 1994. He is the author or co-author of 50 peer-reviewed publications that are classified as

original reports relevant to the study of cardiology, 83 peer-reviewed research publications that are classified as clinical communications, 31 review articles related to cardiology and hypertension and 14 book chapters on cardiology-related topics. As a clinical scientist, he has participated in many landmark clinical trials that have established standard of care principles in the treatment of patients with cardiovascular disease, including pharmacological antiplatelet therapies. He has been recognized with many awards throughout his career.

[38] Dr. Zusman submitted an expert report on issues directly related to validity and infringement of the ‘644 Patent. Portions of his submissions are provided throughout these reasons where they are relevant to the Court’s analysis.

B. *Dr. Timothy Warner*

[39] Dr. Warner is a Professor of Vascular Inflammation and Director of the Blizard Institute at Queen Mary University of London in the United Kingdom. He obtained a BSc in Pharmacology at Chelsea College (later King’s College London) in 1986, and a PhD at the William Harvey Research Institute at the University of London in 1989. He then pursued post-doctoral studies with a leading biochemical pharmacologist at Northwestern University and Abbott Laboratories in Chicago.

[40] In 1992, Dr. Warner returned to the William Harvey Research Institute, becoming a British Heart Foundation basic science lecturer in 1995 and Professor of Vascular Inflammation in 2000. He also served as Deputy Dean for Postgraduate Research in the School of Medicine &

Dentistry (2014-2017) and Deputy Director (Research and Innovation) for the Life Science Initiative of Queen Mary University of London (2015-2017).

[41] His current research involves the interaction between local formed vasoactive mediators (biochemical mediators that cause blood vessels to dilate or constrict), platelets and anti-thrombotic therapies, especially aspirin and ADP-receptor blockers. He has published more than 250 research papers, reviews, articles and abstracts, and is the principal editor of the journal *Platelets*.

[42] Dr. Warner submitted an expert report on issues directly related to validity and infringement of the ‘644 Patent. Portions of his submissions are provided throughout these reasons where they are relevant to the Court’s analysis.

IX. State of the Art

A. *Person of Ordinary Skill in the Art*

[43] The parties’ experts agreed that the person of ordinary skill in the art (“POSITA”) includes a pre-clinical pharmacologist in the area of antithrombotic and antiplatelet drugs; however, they disagreed on whether the POSITA also includes clinicians. Specifically, Dr. Falotico opined that a clinician would not be an ideal person to review the ‘644 Patent because it relates to pre-clinical experiments and data.

[44] I agree with Drs. Warner and Zusman that the POSITA also includes a clinician who treats patients suffering from diseases caused by thrombus and embolus. The focus of the ‘644 Patent is the use of prasugrel and aspirin to prevent and treat diseases caused by thrombus and embolus. Moreover, the ‘644 Patent provides dose ratios for prasugrel and aspirin, as well as upper and lower limit doses based on the symptoms of the patient, and these aspects of the ‘644 Patent are directed at a clinician who is trained to determine the appropriate doses of medicaments for his or her patients.

B. *Common General Knowledge*

[45] Common general knowledge is the knowledge generally known by the POSITA at the claim date (December 25, 2000) when addressing obviousness, or the publication date (July 4, 2002) of the patent when construing the patent’s claims.

[46] What comprises common general knowledge has been articulated by this court in *Eli Lilly v Apotex*, 2009 FC 991 at paragraph 97, aff’d 2010 FCA 240 [*Eli Lilly*] (adopted from *General Tire & Rubber Co v Firestone Tyre & Rubber Co*, [1972] RPC 457, [1971] FSR 417 (UKCA) at 482-483):

> 1) Common general knowledge is distinct from what in patent law is regarded as public knowledge. Public knowledge is theoretical and includes each and every patent specification published, however unlikely to be looked at and in whatever language it is written. Common general knowledge, in contrast, is derived from a common sense approach to the question of what would be known, in fact, to an appropriately skilled person that could be found in real life, who is good at his or her job.
>
> 2) Common general knowledge will include patent specifications that are well known amongst those versed in the art. In particular

> industries, the evidence may show that all patent specifications form part of the relevant knowledge.
>
> 3) Common general knowledge does not necessarily include scientific papers, no matter how wide the circulation of the relevant journal or how widely read the paper. A disclosure in a scientific paper only becomes common general knowledge when it is generally known and accepted without question by the bulk of those engaged in the particular art.
>
> 4) Common general knowledge does not include what has only been written about and never, in fact, been used in a particular art.

[47] With regard to how to prove what comprises common general knowledge, this Court in *Eli Lilly* at paragraph 100, quoted Simon Thorley et al, *Terrell on the Law of Patents*, 16th ed (London: Sweet & Maxwell, 2006):

> Proof of common knowledge is given by witnesses competent to speak upon the matter, who, to supplement their own recollections, may refer to standard works upon the subject which were published at the time and which were known to them. In order to establish whether something is common general knowledge, the first and most important step is to look at the sources from where the skilled addressee could acquire his information.
>
> The publication at or before the relevant date of other documents such as patent specifications may be to some extent prima facie evidence tending to show that the statements contained in them were part of the common knowledge, but is far from complete proof, as the statements may well have been discredited or forgotten or merely ignored. Evidence may, however, be given to prove that such statements did become part of the common knowledge.

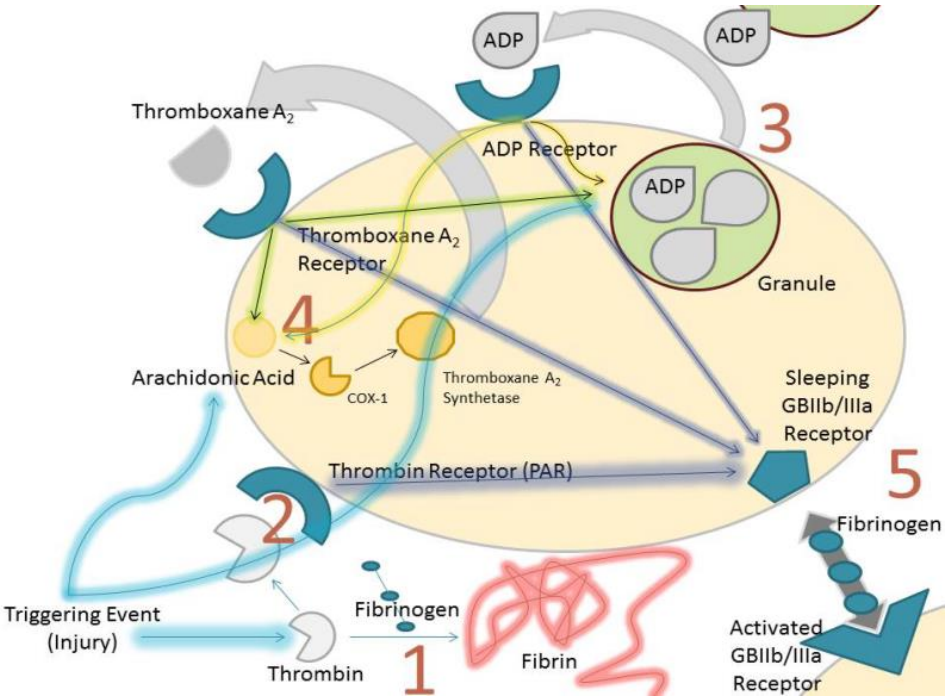
[48] The parties' experts agreed that several features of blood clot formation and treatment constituted common general knowledge as of the claim date:

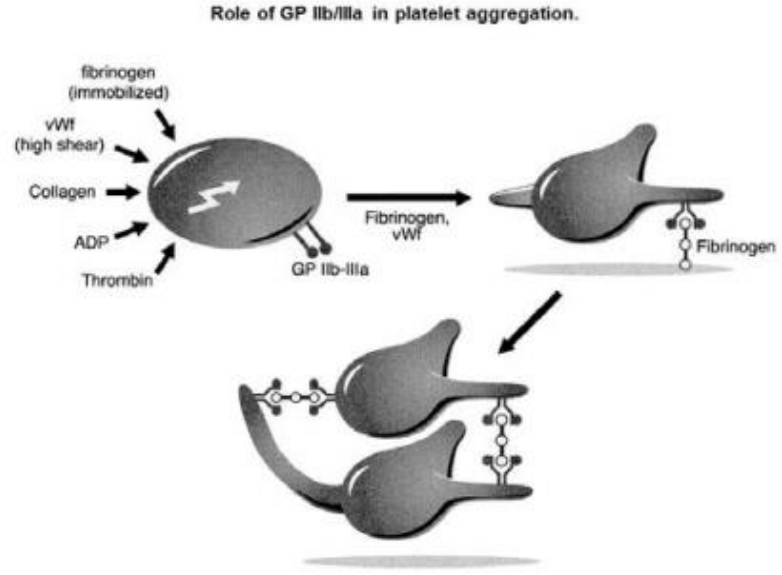
1. Blood clotting (thrombus formation or thrombogenesis) prevents excessive bleeding when a blood vessel is injured. A thrombus is a clot that forms in an artery or vein and an

embolism is a clot that moves in the bloodstream. Thrombus and embolus formation can lead to undesirable and even fatal conditions including unstable angina, myocardial infarction, stroke and transient ischemic attacks.

2. Blood platelets provide a foundation for clotting by binding together to form an initial plug. Once the initial plug is made, blood-borne materials (fibrin) stick together and seal the inside of the wound. This traps more platelets and red blood cells within the plug and starts the healing process.
3. As of the claim date, several physiological pathways of this process were being investigated as potential targets for preventing blood clotting:
4. the enzyme thrombin converts the protein fibrinogen into fibrin;
    a) thrombin also binds to platelets and activates a receptor on the platelet surface known as glycoprotein IIb/IIIa ("GPIIb/IIIa");
    b) when an artery is injured, platelets and injured red blood cells release adenosine diphosphate ("ADP"), which binds to platelets and activates their GPIIb/IIIa receptors;
    c) injury to an artery also causes arachidonic acid to be released from platelets. Arachidonic acid is converted by the enzymes cyclooxygenase 1 (COX-1) and thromboxane synthetase into thromboxane A_2. Thromboxane A_2 binds to platelets and activates their GPIIb/IIIa receptors;
    d) once activated by thrombin, ADP or thromboxane A_2, the GPIIb/IIIa receptor binds fibrinogen to form a platelet aggregate.

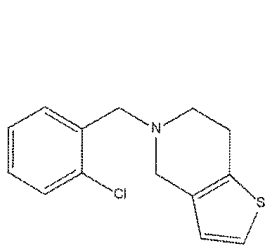
[49] These pathways are illustrated in the diagrams below, as set out on pages 29 and 30 of Dr. Falotico's affidavit:



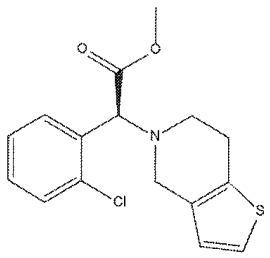


a) The drug acetylsalicylic acid (aspirin) was known to inhibit the thromboxane A_2 pathway through its inhibition of the enzyme COX-1. It was a standard anti-thrombotic treatment by the claim date; however, it was known to cause allergic reactions and gastrointestinal bleeding in some patients.

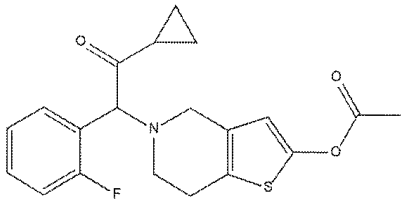
b) As well, a number of agents were known to irreversibly block the ADP-receptor on platelets. Two of these agents, ticlopidine and clopidogrel, had been approved for sale as monotherapies. Ticlopidine had a delayed onset of action and potentially severe side effects. Clopidogrel was more potent and had a shorter onset and less-severe side effects. The third agent, prasugrel, was described in the literature as having a better profile than clopidogrel but it had not yet been approved for sale. Ticlopidine, clopidogrel and prasugrel are structurally related and known as "thienopyridines" because of their fused thiophene and tetrahydropyridine rings:



ticlopidine



clopidogrel



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[50] I agree that all the information in (a) to (e) above formed part of the common general knowledge at the relevant date. There was some disagreement with respect to interpreting the scientific literature that existed at the claim date, involving the relationship between these three

thienopyridines as well as the results of their use in combination with aspirin. The key pieces of prior art relied on by the parties are described below.

C. *Prior Art*

(1) Applicants' Position

[51] The Applicants state that the following articles showed there was no "class effect" among thienopyridines for the treatment of thrombotic diseases:

- Asai et al, "CS-747, a New Platelet ADP Receptor Antagonist" (*Annu Rep Sankyo Res Lab* 1999; 51:1-44) ("Asai et al (1999) #1"); and
- Sugidachi et al, "The *in vivo* pharmacological profile of CS-747, a novel antiplatelet agent with platelet ADP receptor antagonist properties" (*Br J Pharmacol* 2000; 129:1439-1446).

[52] The Applicants also state that the following paper showed that an ideal treatment for thrombotic diseases would bind reversibly, unlike ticlopidine, clopidogrel and prasugrel:

- Smallheer et al, "Chapter 10: Antiplatelet Therapies" (*Annu Rep Med Chem* 2000; 35:103-122).

[53] The Applicants as well state that the following article showed that the combination of clopidogrel and aspirin had shown synergistic potency in clinical studies:

- Herbert et al "The Antiaggregating and Antithrombotic Activity of Clopidogrel Is Potentiated by Aspirin in Several Experimental Models in the Rabbit" (*Thromb Haemost* 1998; 80:512-8).

[54] The Applicants further state that the following prior art showed that the combination of ticlopidine and aspirin did not have a synergistic, anti-thrombotic effect:

- US Patent No. 5,989,578, dated November 23, 1999, entitled "Associations of Active Principles Containing Clopidogrel and an Antithrombotic Agent";
- Canadian Patent No. 1,066,193, dated November 13, 1979, entitled "Therapeutic Composition Having an Inhibiting Activity on Blood Plate Aggregation";
- Farrell et al, "The Lack of Augmentation by Aspirin of Inhibition of Platelet Reactivity by *Ticlopidine*" (*Am J Cardiol* 1999; 83:770-774);
- Uchiyama et al, "Combination Therapy With Low-Dose Aspirin and Ticlopidine in Cerebral Ischemia" (*Stroke* 1989; 20:1643-1647); and
- Rupprecht et al, "Comparison of Antiplatelet Effects of Aspirin, Ticlopidine, or Their Combination After Stent Implantation" (*Circulation* 1998; 97:1046-1052).

(2) Apotex's Position

[55] Apotex states that the following articles showed that combination therapy comprising ticlopidine and aspirin, or clopidogrel and aspirin, had become the standard of care in the treatment of diseases caused by thrombus or embolus:

- Jarvis and Simpson, "Clopidogrel: A Review of its Use in the Prevention of Atherothrombosis" (*Drugs* 2000; 60:347-377); and
- Mishkel et al, "Clopidogrel as Adjunctive Antiplatelet Therapy During Coronary Stenting" (*J Am Coll Cardiol* 1999; 34:1884-90).

[56] Apotex further states that the following articles showed that combination therapy of aspirin with ticlopidine or clopidogrel, took advantage of the complimentary mechanisms of action of thienopyridines and aspirin:

- Uchiyama et al (1989), noted above; and
- Gorelick et al, "Therapeutic Benefit: Aspirin Revisited in Light of Introduction of Clopidogrel" (*Stroke* 1999; 30:1716-1721).

[57] Moreover, Apotex takes the position that the following articles showed that the combination of a thienopyridine with aspirin was safe and effective in the prevention and treatment of diseases caused by thrombus or embolus, and was more effective than each agent alone:

- Uchiyama et al (1989), noted above;
- Van Belle et al, "Two-pronged antiplatelet therapy with aspirin and ticlopidine without systematic anticoagulation: an alternative therapeutic strategy after bailout stent implantation" (*Coron Artery Dis* 1995; 6:341-345);
- Schömig et al, "A Randomized Comparison of Antiplatelet and Anticoagulant Therapy after the Placement of Coronary-Artery Stents" (*N Engl J Med* 1996; 334:1084-9);
- Goods et al, "Comparison of *Aspirin* Alone Versus *Aspirin* Plus *Ticlopidine* After Coronary Artery Stenting" (*Am J Cardiol* 1996; 78:1042-1044);
- Lecompte et al, "Antiplatelet Effects of the Addition of Acetylsalicylic Acid 40 Mg Daily to Ticlopidine in Human Healthy Volunteers" (*Clin Appl Thromb Hemost* 1997; 3:245-250);

- Neumann et al, "Antiplatelet Effect of Ticlopidine After Coronary Stenting" (*J Am Coll Cardiol* 1997; 29:1515-9);
- Leon et al, "A Clinical Trial Comparing Three Antithrombotic-Drug Regimes After Coronary Artery Stenting" (*N Engl J Med* 1998; 339:1665-71);
- Urban et al, "Randomized Evaluation of Anticoagulation Versus Antiplatelet Therapy After Coronary Stent Implantation in High-Risk Patients" (*Circulation* 1998; 98:2126-2132);
- Moussa et al, "Effectiveness of Clopidogrel and Aspirin Versus Ticlopidine and Aspirin in Preventing Stent Thrombosis After Coronary Stent Implantation" (*Circulation* 1999; 99:2364-2366);
- Mishkel et al (1999), noted above;
- Muller et al, "A Randomized Comparison of Clopidogrel and Aspirin Versus Ticlopidine and Aspirin After the Placement of Coronary-Artery Stents" (*Circulation* 2000; 101:590-593);
- Moshfegh et al, "Anitplatelet Effects of Clopidogrel Compared With Aspirin After Myocardial Infarction: Enhanced Inhibitory Effects of Combination Therapy" (*J Am Coll Cardiol* 2000; 36: 699-705);
- Betrand et al, "Double-Blind Study of the Safety of Clopidogrel With and Without a Loading Dose in Combination With Aspirin Compared With Ticlopidine in Combination With Aspirin After Coronary Stenting" (*Circulation* 2000; 102:624-629); and
- Bossavy et al, "A Double-Blind Randomized Comparison of Combined Aspirin and Ticlopidine Therapy Versus Aspirin or Ticlopidine Alone on Experimental Arterial Thrombogenesis in Humans" (*Blood* 1998; 92:1518-1525).

[58] Apotex also states that the following articles showed that the combination of a thienopyridine with aspirin produced a synergistic antiplatelet/antithrombotic effect:

- Canadian Patent No. 1,066,193, noted above;
- US Patent No. 5,989,578, noted above;
- Rupprecht et al (1998), noted above;
- Moshfegh et al (1998), noted above;
- Herbert et al (1998), noted above;
- Harker et al, "Clopidogrel Inhibition of Stent, Graft, and Vascular Thrombogenesis With Antithrombotic Enhancement by Aspirin in Nonhuman Primates" (*Circulation* 1998; 98:2461-2469);
- Quinn and Fitzgerald, "Ticlopidine and Clopidogrel" (*Circulation* 1999; 100:1667-1672); and
- Cadroy et al, "Early Potent Antithrombotic Effect With Combined Aspirin and a Loading Dose of Clopidogrel on Experimental Arterial Thrombogenesis in Humans" (*Circulation* 2000; 101:2823-2828).

[59] Finally, Apotex states that the following prior art showed that prasugrel was the third generation thienopyridine developed, exhibiting certain advantages over clopidogrel and ticlopidine, and that prasugrel was expected to be useful for the prevention of thrombotic diseases and to have a similar ratio of benefit/bleeding risk as clopidogrel:

- Canadian Patent No. 2,077,695, filed on September 8, 1992, entitled "Hydropyridine Derivatives Having Antithrombotic Activity";

- Asai et al, "Antithrombotic and Antiplatelet Effects of CS-747, a Novel P2T Antagonist" (*J Thromb Haemost*, 1999 (Supp) p 829) ("Asai et al (1999) #2");
- Asai et al (1999) #1, noted above; and
- Sugidachi et al (2000), noted above.

X. Claim Construction

[60] The relevant date for construing the claims of the '644 Patent is the date of publication: July 4, 2002.

[61] Construction is a question of law for the Court and should be done before considering infringement or validity. The Supreme Court determined the canons of claim construction in a trilogy of cases: *Whirlpool Corp v Camco Inc*, 2000 SCC 67 [*Whirlpool*] at paras 49-55; *Free World Trust v Électro Santé Inc*, 2000 SCC 66 at paras 44-54; and *Consolboard Inc v MacMillan Bloedel (Saskatchewan) Ltd*, [1981] 1 SCR 504 at para 27.

[62] Those decisions state that:

a) claims are to be read in an informed and purposive way, with a mind willing to understand and viewed through the eyes of the POSITA, as of the date of publication, having regard to the common general knowledge;
b) adherence to the language of the claims allows them to be read in the manner in which the inventor is presumed to have intended, and in a way that is sympathetic to

accomplishing the inventor's purpose, which promotes both fairness and predictability; and

c) the whole of the specification should be considered, in order to ascertain the nature of the invention, and the construction of the claims must be neither benevolent nor harsh, but instead should be reasonable and fair to both the patentee and the public.

[63] While experts may aid the Court in construing terms or elements of the claims, that assistance is only necessary when the Court deems it helpful or useful to do so – if the meaning of terms is evident from the patent specification, the Court does not need the advice of experts.

[64] The parties are in general agreement on the construction of the Asserted Claims.

[65] Claim 22, as it depends from claims 18 and 20, comprises the following elements:

- use of prasugrel or a pharmaceutically acceptable salt thereof;
- in the preparation of a medicament;
- for simultaneous, but separate, administration with aspirin;
- for the prevention of treatment of a disease caused by thrombus or embolus.

[66] Claim 29 comprises the following elements:

- prasugrel or a pharmaceutically acceptable salt thereof;
- for use in combination with aspirin;
- in preventing or treating disease caused by thrombus or embolus.

[67] Claim 29 does not specify whether the administration of prasugrel and aspirin must be simultaneous or sequential; therefore, both possibilities may purposively be included. While the parties agree that "sequential" means that one agent must be given before or after the other, there is a dispute as to whether the POSITA would understand the appropriate time interval between the administrations of the two agents. That issue is discussed in more detail below with respect to insufficiency and claims broader than the invention made or disclosed.

[68] As well, the parties and their experts disagree on whether claims 22 and 29 incorporate the notion that prasugrel combined with aspirin produces a synergistic effect with respect to the prevention and treatment of thrombosis. This is also discussed in more detail below, in relation to patentable subject matter and obviousness.

XI. Validity

A. *Burden*

[69] The presumption of validity in subsection 43(2) of the *Patent Act*, RSC 1985, c P-4 [*Patent Act*] is weak and once Apotex adduces evidence that has an "air of reality" to rebut that presumption, the legal burden shifts to the Applicants to establish on a balance of probabilities that each of the allegations of invalidity asserted are not justified (*Meda AB v Canada (Health),* 2016 FC 1362 at para 52).

[70] The parties agree that the Applicants must prove on a balance of probabilities that Apotex's allegation of invalidity is not justified.

B. *Patentable Subject Matter*

[71] Combinations of compositions of matter and their use are patentable if the claimed subject matter is new, useful and non-obvious (*Bridgeview Manufacturing Inc v 931409 Alberta Ltd (Central Alberta Hay Centre)*, 2010 FCA 188 [*Bridgeview*] at paras 6-12, 51).

[72] However, it is essential to the validity of a patent for a combination that the combination should lead to a unitary result, and that such result should be different from the sum of the results of the elements (*R v American Optical Co* (1950), 13 CPR 87 at 98-99 (Ex CR)).

[73] Apotex alleges that the claims of the ‘644 Patent are invalid, void and of no force or effect as they claim a “mere aggregate and not a patentable combination”, thus failing to meet the definition of an invention under section 2 of the *Patent Act*. The “purported invention” relates to an additive combination of prasugrel plus aspirin – the use of prasugrel plus aspirin does not produce a new or different result as compared to their separate uses.

[74] Apotex also states that the Asserted Claims are not restricted to combinations of prasugrel and aspirin that exhibit a synergistic effect. Nowhere in the disclosure of the ‘644 Patent is there an assertion that the combination of prasugrel and aspirin exhibits a synergistic effect. At most, there are data in Table 1 on page 8 of the ‘644 Patent that can arguably support an assertion of synergy. While the evidence on this point is contradictory, based upon the totality of the evidence adduced, the Applicants have not met their burden in respect of this issue.

[75] The Sankyo Reports, referred to by Drs. Sugidachi and Ogawa, reveal the following:

- Sankyo Report 1 described the *ex vivo* effect of prasugrel in combination with aspirin on platelet aggregation in rats. The authors found that prasugrel in combination with aspirin showed [redacted]
- Sankyo Report 2 described the effect of the combination of prasugrel and aspirin in rats: (1) on thrombus formation in an AV-shunt model; and (2) on prolongation on bleeding time. The authors concluded that the combination of prasugrel with aspirin resulted in [redacted] Some of the methods and data from this study were disclosed in the '644 Patent;
- Sankyo Report 3 described the antiplatelet effects of prasugrel in combination with aspirin using an *ex vivo* dog platelet model. The authors found that the combined use of prasugrel with aspirin produced [redacted]; and
- Sankyo Report 4 compared the combined effect of prasugrel and aspirin on rat *ex vivo* platelet aggregation to that of clopidogrel and aspirin. The authors found that [redacted]

[76] Statements in the '644 Patent relating to the effect of the combination of prasugrel and aspirin include:

- "possess excellent inhibitory activity against platelet aggregation and thrombogenesis" (page 3b, final paragraph);

- "results in more potent effectiveness than the use of each component alone" (page 4, second paragraph); and
- "the therapeutic effect of the compound administered later is expected to add to the therapeutic effects of the previously administered component" (page 4, third paragraph).

[77] At pages 6-8 of the '644 Patent, under "Example 1", is a brief summary of the methods used in Sankyo Report 2, which described the inhibitory effect of prasugrel and aspirin against thrombus formation using an AV-shunt model in rats. Some of the data from that study is shown in Table 1 on page 8 of the '644 Patent, which is reproduced below:

[Table 1]

Compounds		Thrombus Weight	Inhibition Rate
Compound A (mg/kg)	Aspirin (mg/kg)	(mg)	(%)
0	0	52.3 ± 1.2	-
0	10	46.6 ± 2.8	12.3 ± 4.4
0.3	0	43.5 ± 2.1	17.0 ± 4.1
0.6	0	37.5 ± 2.1	28.3 ± 4.0
0.3	10	30.5 ± 3.5	41.8 ± 6.6
0.6	10	23.2 ± 3.8	55.7 ± 7.2

Compound A: 2-Acetoxy-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine

[78] Dr. Falotico opined that the results in Table 1 demonstrate the following:

- the mean inhibition rates (percent inhibition of thrombus formation compared to the control) with a 0.3 mg/kg dose and a 0.6 mg/kg dose of prasugrel alone are 17% and 28.3% respectively;

- for a 10 mg/kg dose of aspirin alone, the inhibition rate was 12.3%;
- when 10 mg of aspirin was administered in combination with either 0.3 mg/kg or 0.6 mg/kg of prasugrel, the inhibition rate was 41.8% and 55.7% respectively. This represents an effect that is more than additive, as an additive effect in this test would have been 29.3% (the sum of 12.3% and 17.0%) for the combination of 10 mg/kg aspirin and 0.3 mg/kg prasugrel and 40.6% (the sum of 12.3% and 28.3%) for the combination of 10 mg/kg aspirin and 0.6 mg/kg prasugrel;
- the effect of aspirin and prasugrel was dose dependent, i.e., the effect was greater when aspirin was combined with a 0.6 mg/kg dose of prasugrel than when combined with a 0.3 mg/kg dose of prasugrel (i.e., 15.1% more versus 12.5% more inhibition of thrombus formation). Both combinations gave a substantial benefit versus the agents alone; and
- overall, the data teach that the use of prasugrel in combination with aspirin produces excellent inhibitory activity against platelet aggregation that is greater than the sum of the effects of each agent alone (i.e., synergy).

[79] Dr. Falotico also opined that, after reading the ‘644 Patent in its entirety, it would be clear to the POSITA that the invention relates to the use of prasugrel and aspirin in combination to achieve an antiplatelet/antithrombotic effect that is greater than the sum of such effects with each agent alone. His opinion was based on the fact that the data in Table 1 was disclosed in the ‘644 Patent.

[80] Dr. Falotico further opined that the data in the Sankyo Reports also supported and bolstered the inventive feature (a more than additive antiplatelet/antithrombotic effect) of

prasugrel in combination with aspirin. Each of the *ex vivo* antiplatelet studies conducted by Sankyo pointed to the same conclusion, namely, that combining prasugrel with aspirin has a more than additive antiplatelet effect, and it was shown in more than one warm-blooded animal species.

[81] Dr. Warner disagreed with Dr. Falotico's interpretation of the data in the '644 Patent. He explained that:

> …determining whether a combination of drugs exhibits synergy requires more than just comparing the activity of the combination to the sum of the activities of the individual compounds. Testing for synergy requires determination of the potency of the combination and comparison of this potency with that of a theoretically additive combination. It is important that each drug demonstrates a dose-dependent common effect that can be quantified when the drugs are tested individually or in combination. Essentially, one compares the dose-response curve of the mixture with that of the theoretical curve of additivity in the same proportional mix. Further, synergism is not only a feature of the drugs and the test; it depends as well on the mixture ratio of the two components in the combination. There also needs to be a statistical analysis of whether or not the data show a statistically synergistic effect. Thus, the testing and data provided in the 644 patent are insufficient to demonstrate whether the combination of prasugrel and aspirin exhibit a synergistic antithrombotic effect (or synergistic inhibitory activity against platelet aggregation).

[82] Dr. Warner also disagreed with Dr. Falotico that the POSITA would understand that the invention relates to the use of prasugrel and aspirin in combination to achieve an antiplatelet/antithrombotic effect that is greater than the sum of such effects with each agent alone. He wrote:

> In addition to my comments directly above as to how the data in the 644 patent do not demonstrate a greater than additive effect, or synergy, nowhere else in the 644 patent is there a statement suggesting that the combination of prasugrel and aspirin achieve an

> antiplatelet/antithrombotic effect that is greater than the sum of such effects with each agent alone. Rather, the 644 patent states that "the use in combination of [prasugrel] … and aspirin, results in more potent effectiveness than the use of each component alone" and "the therapeutic effect of the compound administered later is expected to add to the therapeutic effects of the previously administered component" (page 4), suggesting additive activity. Further, there is no reference to a greater than additive, or synergistic, effect in the Relevant Claims, or in any other claims of the '644 Patent.

[83] Dr. Zusman agreed with Dr. Warner that the POSITA would understand the '644 Patent to mean that combining prasugrel and aspirin has an additive effect. He referred to the same quotes from the '644 Patent noted by Dr. Warner, and opined that the inventors are stating that the effect is additive. The inventors did not state that their invention was the achievement of an antiplatelet/antithrombotic effect that is greater than the sum of such effects with each agent alone.

[84] Dr. Zusman also agreed with Dr. Warner that neither the inventors nor the POSITA would interpret the data provided in Table 1 to indicate that the combination of prasugrel and aspirin provided a synergistic effect. This is because synergy is not simply assessed as "a more than additive effect" as Dr. Falotico presented. The POSITA would know that the determination of drug synergism is a quantitative pursuit that involves a rigorous demonstration that the combination effect is greater than that which is expected from the individual drugs' potencies. By December 2000, there were statistical methods available to the POSITA to assess synergism in the combination of drugs. The inventors did not include such quantitative statistical analysis for the determination of a synergistic effect in the '644 Patent, nor did they state that they have done so. Furthermore, Dr. Falotico did not perform such an analysis with the Table 1 data, but he

had previously performed such an analysis in a paper he published relating to the use of clopidogrel with aspirin.

[85] While there is ambiguity in claims 22 and 29 as to whether either claim covers the synergistic effect produced by prasugrel combined with aspirin, I agree with the Applicants that the ‘644 Patent as a whole, when read purposively with a mind willing to understand, disclosed patentable subject matter. The combination of prasugrel and aspirin was a new and useful treatment for diseases caused by thrombus or embolus, in that it possessed new, useful and synergistic inhibitory activity against platelet aggregation, without unacceptable bleeding risks or other side effects.

[86] I do not agree with Apotex that in reaching that conclusion I must “read in” synergistic effects to the ‘644 Patent disclosure to find a new and useful invention, as I cautioned against in *Bristol-Myers Squibb Canada v Apotex Inc*, 2017 FC 296 at paragraph 191.

[87] While much was said about the use of statistical models to distinguish between synergistic and additive effects, the fact that the combination of prasugrel and aspirin was a new and useful treatment is not dispute. The four Sankyo Reports all showed [redacted], and in two of those studies the authors went so far as to definitively call the results [redacted]. Drs. Warner and Zusman were concerned that the reports did not include statistical analyses to confirm synergy, but that point is not determinative and they never stated that the results were not new and useful.

[88] Indeed, on cross-examination Dr. Warner admitted that when the data in Table 1 of the ‘644 Patent are examined at face value, without considering statistics or variability, the combination of prasugrel plus aspirin produced a numerically greater inhibition rate than prasugrel and aspirin alone. As well, Dr. Warner had previously stated that some studies in the prior art showed synergy, but then admitted that no statistical analysis had been done in those studies, including in a paper he co-authored.

[89] Dr. Zusman made a similar admission during his cross-examination, that the data in Table 1 showed synergy if one only looks at the means without taking into consideration the dispersion of the data.

[90] The ‘644 Patent, when read purposively with a mind willing to understand, discloses that the use of prasugrel combined with aspirin results in an effect on platelet aggregation that is new, useful and more than the mere sum of the effects of the two agents taken alone.

[91] I find that the ‘644 Patent discloses patentable subject matter.

C. *Obviousness*

[92] The relevant date for assessing obviousness is the claim date, which is the priority date of December 25, 2000.

[93] Section 28.3 of the *Patent Act* requires the subject matter of a claim to not have been obvious on the claim date. The Supreme Court of Canada set out a four-part test for obviousness in *Apotex Inc v Sanofi-Synthelabo Canada Inc*, 2008 SCC 61 [*Sanofi*] at paragraph 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?

[94] At the fourth stage of this test, the issue of “obvious to try” may arise, that is, whether it was more or less self-evident to try to obtain the invention – the mere possibility that something might turn up is not enough (*Sanofi* at paras 64, 66 and 67). If an “obvious to try” test is warranted, factors to be taken into consideration include (*Sanofi* at para 69):

- Was it more or less self-evident that what was being tried ought to work? Were there a finite number of identified predictable solutions known to persons skilled in the art?
- What was the extent, nature and amount of effort required to achieve the invention? Were routine trials carried out or was the experimentation prolonged and arduous, such that the trials would not be considered routine?
- Was there a motive provided in the prior art to find the solution the patent addresses?

[95] In this case, the "obvious to try" issue is applicable.

[96] Obviousness is a difficult test to meet. The Court is cautioned that expert witnesses may unknowingly be biased by hindsight (*Bridgeview* at para 50).

[97] There is some argument between the parties on whether the Federal Court of Appeal has recently qualified the test for obviousness and use of the inventive concept, as established by the Supreme Court in *Sanofi* and *Teva Canada Ltd v Pfizer Canada Inc*, 2012 SCC 60 [*Teva*], in the decisions of *Ciba Specialty Chemicals Water Treatments Ltd v SNF Inc*, 2017 FCA 225 [*Ciba*] at paragraphs 72-77, and *Bristol-Myers Squibb Canada Co v Teva Canada Limited*, 2017 FCA 76 at paragraphs 62-68.

[98] I do not find that those decisions qualify the approach to determining obviousness when read purposively in light of the Supreme Court's *Sanofi* and *Teva* approaches. Rather, when the Court has regard to section 28.3 of the *Patent Act* and both the *Sanofi* and *Teva* decisions, the focus in deciding whether an invention as claimed is obvious should be on the claim(s) itself/themselves, unless there is ambiguity in the claim(s) under consideration, and only then is it necessary to refer to the disclosure to help understand whether an invention as claimed is obvious or not over the prior art.

[99] The Applicants also raise the issue that the prior art relied upon by Apotex in its NOA and put to their experts was curated with hindsight and the experts were unaware of how it was

assembled. Moreover, the experts conducted their own searches but did not disclose those searches or any relevant prior art beyond that relied upon in the NOA.

[100] I agree with Apotex that the criticisms are without merit or are irrelevant. I endorse the comments of Justice Zinn in *Allergan Inc v Apotex Inc*, 2016 FC 344 at paragraphs 20 and 21:

> [20] Allergan submits that the 49 references cited in Apotex's NOA are not representative of the common general knowledge because they were collected by Apotex, with the benefit of hindsight, and with a view to invalidating the 632 Patent. Moreover, it notes that Apotex's two experts did no independent prior art search.
>
> [21] I agree with Apotex that these objections are without merit. Apotex's experts provided reasons as to why these references would have been easily located during a prior art search or stated that they would already have been known to the POSITA. Dr. Sheardown attests that "many of the documents are well-known references in the field of pharmaceutical formulation, in particular the field of ophthalmic formulations," that she is familiar with many of the articles and texts, and that any of the others would have been easily located by a formulator conducting a diligent search in 1998. More importantly, Allergan has offered no evidence that there are other material references constituting the prior art that are not included in the NOA, or that those referenced in the NOA do not constitute the common general knowledge.

[101] Turning to the merits of the obviousness analysis, I must answer the question of whether the subject matter of the two claims in issue, claims 22 and 29, as properly construed, would be obvious in view of the prior art and common general knowledge of the POSITA at the claim date. In other words, would the POSITA come directly and without difficulty to the solution that the combination of prasugrel and aspirin simultaneously (claim 22) or simultaneously or sequentially (claim 29), would have an enhanced, non-obvious effect on preventing or treating a disease caused by thrombus or embolus.

(1) Claim date, POSITA, common general knowledge and state of the art

[102] All of these points are addressed above at paragraphs 43-59.

(2) Inventive concept of claims 22 and 29

[103] The Applicants' position on the inventive concept is that the combination of prasugrel and aspirin is useful for the prevention or treatment of thrombotic diseases and elicits an antiplatelet/antithrombotic effect that is greater than the sum of such effects with the use of each agent alone. In other words, there is "synergistic" or more than additive inhibitory activity in the claimed combinations. This becomes apparent when one reviews Table 1 of the '644 Patent, which shows that the combined use of prasugrel and aspirin has a synergistic effect on inhibition rate and thrombus weight in a warm-blooded animal.

[104] Apotex's position is that the inventive concept is that the combination of prasugrel and aspirin is useful for the prevention and treatment of thrombotic diseases (i.e., synergy does not form part of the inventive concept). Apotex rejects the Applicants' view of the inventive concept for a number of reasons:

1) Dr. Falotico's testimony suggests that he did not adhere to the Supreme Court's direction that recourse to the disclosure to ascertain the inventive concept is only permissible in limited circumstances;
2) on cross-examination, Dr. Falotico admitted that the claims were clear and understandable to the skilled person;

3) the Applicants' position impermissibly narrows the claims – the claims do not only cover compositions that deliver synergistic results, but any combination of prasugrel and aspirin;
4) the Applicants' "inventive concept" represents a conclusion based upon data in circumstances where the inventors did not draw such a conclusion – the '644 Patent instead describes an additive effect;
5) the Applicants' position that the inventive concept includes a synergistic effect in the context of a patent that makes no such assertion has to be considered in light of the Applicants' counsel's submission that synergy is an unclear term, meaning different things to different people; and
6) Apotex's expert evidence established that the data presented in the '644 Patent were insufficient to reach a conclusion as to synergy.

[105] While there is some ambiguity in whether the Asserted Claims cover the synergistic effect produced by prasugrel combined with aspirin, as evidenced by the experts' testimony in helping to understand claim 22 and 29, I find that the '644 Patent and the Asserted Claims, read purposively, demonstrate that prasugrel plus aspirin has an antithrombotic effect that is greater than the sum of the effects of each agent alone. The POSITA would have understood this inventive concept in light of the common general knowledge and the patent as a whole. Table 1 of the '644 Patent shows that the combined use of prasugrel plus aspirin has a synergistic effect on inhibition rate in a warm-blooded animal. Apotex's experts did not describe the data in Table 1 as more than additive in their affidavits, but admitted that when the data are examined at face

value, without considering statistics or variability, the combination produced a numerically greater inhibition rate than prasugrel or aspirin alone.

(3) Differences between the prior art and the inventive concept

[106] The Applicants state that the differences between the prior art and the inventive concept of the Asserted Claims are:

a) there was no prior art suggesting the use of prasugrel and aspirin; there was a gap in the knowledge between the state of the art and inventive concept of the Asserted Claims;
b) the combined effect of prasugrel plus aspirin was unknown and could not have been predicted in advance; there were a number of alternative pathways and mechanisms of action;
c) there was no motivation to combine prasugrel and aspirin; the potential benefits were unknown and there were significant concerns about bleeding rates; and
d) the invention required significant time, effort and resources and the underlying work was not routine.

[107] Apotex asserts that the only difference was that, while ticlopidine and clopidogrel had been combined with aspirin to treat and prevent diseases caused by thrombus or embolus, there had not yet been a disclosure of the combination of the third generation thienopyridine, prasugrel, with aspirin. Moreover, the total time for testing was at most two weeks to ascertain the potential use of the combination of prasugrel and aspirin, and the testing was routine.

[108] I find that the evidence shows that, as acknowledged by the parties, while the first and second thienopyridines, ticlopidine and clopidogrel, had been combined with aspirin to treat and prevent diseases caused by thrombus or embolus, there had not been a disclosure of the use of the third generation thienopyridine, prasugrel, with aspirin.

[109] However, as described in more detail below, inhibiting two known platelet activation pathways with a thienopyridine and aspirin was known to result in improved therapies. As well, the results of substituting one thienopyridine for another to use in combination with aspirin had been positive.

(4) Whether those differences constitute steps that would have been obvious

[110] The Applicants argue that the use of prasugrel and aspirin was not suggested anywhere in the prior art, and that ticlopidine, clopidogrel and prasugrel have different chemical structures and metabolic pathways.

[111] Moreover, the Applicants state that the effect of combining prasugrel and aspirin was unpredictable at the claim date, synergy was not a "class effect" of thienopyridines, and it was not self-evident that a combination of prasugrel and aspirin would be useful for the prevention or treatment of thrombotic diseases or that synergy would be observed:

- synergy was not observed consistently with ticlopidine plus aspirin and the safety profile of clopidogrel plus aspirin had not been confirmed by the claim date;

- the mechanism of synergy for clopidogrel plus aspirin was (and still is) unknown. There was no line of reasoning to predict that prasugrel plus aspirin would be synergistic based on prior observations with clopidogrel plus aspirin; and
- the efficacy and side effects of an ADP inhibitor with aspirin needed to be determined experimentally. It was not very plain or self-evident that any such studies would work, let alone produce synergy.

[112] Finally, the Applicants' position is that while there was a general motivation in the art to find new antiplatelet therapies, the focus was on agents with reversible platelet binding properties, not on thienopyridines or new combination therapies. There was no motivation to replace clopidogrel with prasugrel in aspirin combination therapy. Moreover, a significant amount of time and effort was required to arrive at the claimed invention, and the research was not routine due to the level of skill and expertise required to conduct experiments with the AV-shunt model.

[113] Apotex counters that its experts provided evidence that the combination of prasugrel and aspirin would have been arrived at by the POSITA without exercising any inventive ingenuity:

- inhibiting two known platelet activation pathways with a thienopyridine and aspirin was an obvious therapeutic target;
- substitution of one thienopyridine for another in combination with aspirin had already succeeded when clopidogrel replaced ticlopidine as the standard of care; and
- it would be obvious to try substituting prasugrel into that combination: the combination of prasugrel and aspirin was one of a handful of therapeutic targets; it was self-evident

that the combination would be useful to treat and prevent diseases caused by thrombus or embolus; trials would have been quick and routine; and the POSITA was motivated to develop the combination for its expected therapeutic benefit.

[114] With respect to the Applicants' asserted inventive concept, Apotex submits that the only difference between the state of the art/common general knowledge and that inventive concept was that the synergistic effect of the combination of prasugrel and aspirin had not been confirmed:

- Apotex's experts opined that synergy would have been obvious to the skilled person and, in any event, would have been obvious to try;
- Dr. Falotico's opinion was premised upon misunderstandings of Canadian law and/or erroneous statements as to the prior art; and
- all testing was routine and was based on previously published work with ticlopidine and clopidogrel in combination with aspirin, and the evidence of the inventors and Dr. Falotico does not support the Applicants' assertions as to the time and complexity of the work giving rise to the claimed invention.

[115] In my view, there are no material differences that would not have been obvious having regard to what was known in the prior art and what is claimed in claims 22 and 29. It was self-evident to try, and the POSITA would reasonably have expected that combining the third generation thienopyridine, prasugrel, with aspirin, simultaneously or sequentially, would produce a beneficial, complementary mechanism of action.

[116] There was a clear motive from the prior art to find the solution of the ‘644 Patent. As noted above, inhibiting two known platelet activation pathways by use of a thienopyridine combined with aspirin was known to result in improved therapies, including synergistic effects. While there was inconsistency in the prior art as to whether the use of ticlopidine with aspirin produced synergistic effects, both parties acknowledged that the use of clopidogrel with aspirin did.

[117] Moreover, the results of substituting one thienopyridine for another to use in combination with aspirin had been positive. Clopidogrel with aspirin was shown to be just as effective, if not better, than ticlopidine with aspirin, which was a standard antiplatelet therapy for the prevention of thrombotic complications after stent implantation (Mishkel et al, 1999 and Jarvis and Simpson, 2000). As such, clopidogrel with aspirin was widely used for the prevention of atherothrombosis after stent implantation (Jarvis and Simpson, 2000).

[118] Conducting tests to confirm the benefits of prasugrel and aspirin was an obvious step forward [redacted]. Although Dr. Falotico opined that the experiments required a high level of expertise, skill and dexterity, he also admitted that the AV-shunt model described in the ‘644 Patent was based on a well-known and validated model described in the literature, including in a study on the antithrombotic effects of clopidogrel and aspirin (Herbert et al, 1998). While these tests did require expertise, the POSITA would have known how to conduct these tests and analyze the results.

[119] Finally, although the effects of the combined use of prasugrel and aspirin could not be predicted with exact certainty, due to the lack of knowledge of metabolic pathways of thienopyridines as well as potential mechanisms of synergy, the POSITA could reasonably expect to achieve the same synergistic, therapeutic effect that was shown in the prior art with respect to clopidogrel (and potentially ticlopidine) combined with aspirin.

[120] As Justice Hughes stated in *Shire Biochem Inc v Canada (Health)*, 2008 FC 538 at paragraph 80, "the existence of a number of possible routes to solve a problem does not mean that the route taken was not obvious." This statement was endorsed by Justice Barnes in *Janssen Inc v Teva Canada Limited*, 2015 FC 184 [*Janssen*] at paragraph 113. Justice Barnes also endorsed the notion that "a route may be an obvious one to try even if it is not possible to be sure that taking it will produce success, or sufficient success to make it commercially worthwhile" (*Janssen* at para 113, citing *Brugger v Medic-Aid Ltd*, [1996] RPC 635 at p 661).

[121] Given that there was a clear motive from the prior art to find the solution of the '644 Patent, that testing was done relatively quickly and based on well-known models, and the reasonable expectation that the combination of prasugrel and aspirin would produce results similar to those that were observed when clopidogrel or ticlopidine was combined with aspirin, it was more or less self-evident and obvious to try the combination of prasugrel with aspirin.

[122] I find that claims 22 and 29 were obvious and therefore invalid.

D. *Sufficiency*

[123] Paragraph 27(3)(a) of the *Patent Act* requires a patent specification to "correctly and fully describe the invention and its operation or use as contemplated by the inventor". The relevant date for assessing whether this requirement was met is the filing date: December 20, 2001.

[124] The test for sufficiency of disclosure is whether the specification:

a) answers the question "what is the invention?";
b) answers the question "how does it work?"; and
c) enables the skilled person to produce the invention using only the instructions contained in the disclosure.

(*Teva* at paras 69-71).

[125] As well, the skilled person can rely on common general knowledge to understand the specification and to apply the patent sensibly (*Whirlpool* at para 53).

[126] Apotex alleges that the specification of the '644 Patent is insufficient because it does not provide the POSITA with the required information as to how to administer prasugrel and aspirin sequentially. In particular, the '644 Patent explicitly states that "the maximum intervals between administration of the two components that can be expected to elicit significant effects could be confirmed by clinical trials or animal studies" ('644 Patent, pp 4-5).

[127] In other words, Apotex's position is that the '644 Patent fails to disclose how to administer prasugrel and aspirin sequentially, by failing to specify the appropriate time interval between administering the two agents. The POSITA would not know what that interval should be without determining it experimentally. Where the POSITA must engage in a minor research project to obtain the invention, a patent disclosure is insufficient (*Teva* at paras 74-75).

[128] However, the experts understood how to put the invention into practice using only the '644 Patent and their common general knowledge. Dr. Falotico explained that the '644 Patent states that aspirin and prasugrel bind irreversibly to platelets and therefore plasma levels of the two agents do not need to be maintained at a certain level during the same period in order to produce their effects. As such, the agents do not have to be given at the same time. The POSITA would have understood that as long as aspirin and prasugrel were both administered within the life-span of the platelet, they would exert an effect. The life-span of a platelet was known to be 6-10 days.

[129] Dr. Zusman agreed on cross-examination that if prasugrel and aspirin were administered during the life of the platelet (i.e., 6-10 days), then they would both have an effect. Dr. Warner also admitted on cross-examination that he understood the temporal limits of sequential administration in the context of the '644 Patent.

[130] I find that the disclosure is sufficient to enable the POSITA to put the invention as claimed in claims 22 and 29 into practice with only the '644 Patent and the common general knowledge available at the relevant date.

E. *Claims broader than the invention made or disclosed*

[131] Subsection 27(4) of the *Patent Act* requires patent claims to define distinctly and in explicit terms the subject-matter of the invention for which an exclusive privilege or property is claimed. A claim is overbroad if it claims more than the invention made or disclosed (*Pfizer Canada Inc v Canada (Minister of Health)*, 2007 FCA 209 at para 115).

[132] Apotex alleges, for the same reason underlying its allegation of insufficiency, that claim 29 is overbroad because it allows for prasugrel and aspirin to be administered sequentially but the inventors did not invent or describe the maximum time interval for sequential administration.

[133] For the same reasons I find that the patent disclosure is sufficient, I also find that claim 29 is not overly broad.

XII. Costs

[134] Costs to the Respondent Apotex, to be assessed at the middle of Column IV of Tariff B.

[135] No costs are recoverable for in-house counsel, employees of the parties, law clerks, students and support staff.

[136] Costs are recoverable only for those experts who provided affidavits or reports that were filed in the proceedings (the "allowable experts"). The hourly rate for allowable experts shall not exceed the hourly rate of senior counsel. Fees paid to allowable experts for time not spent

preparing the expert's affidavit/report or preparing for the expert's own cross-examination are recoverable only where it is demonstrated that it was reasonable and necessary to provide technical assistance to counsel.

[137] Counsel fees shall be based on the basis of:

a) One senior and one junior counsel at the hearing;
b) One senior and one junior counsel in conducting cross-examinations; and
c) One senior counsel in defending cross-examinations.

[138] Travel and accommodation expenses will be assessed on the basis of economy fares, except for overseas travel, and standard rooms in business class hotels based on single occupancy. Business class airfare shall be recoverable for overseas travel.

[139] Photocopying costs will be assessed at $0.25 per page and the number of recoverable copies shall be limited to that which is reasonable and necessary.

[140] Costs are recoverable for all other disbursements reasonably incurred (e.g., transcripts, translation services, computer searches).

JUDGMENT in T-1734-16

THIS COURT'S JUDGMENT is that:

1. The Application is dismissed;
2. Costs to the Respondent Apotex, to be assessed at the middle of Column IV of Tariff B.
3. No costs are recoverable for in-house counsel, employees of the parties, law clerks, students and support staff.
4. Costs are recoverable only for those experts who provided affidavits or reports that were filed in the proceedings (the "allowable experts"). The hourly rate for allowable experts shall not exceed the hourly rate of senior counsel. Fees paid to allowable experts for time not spent preparing the expert's affidavit/report or preparing for the expert's own cross-examination are recoverable only where it is demonstrated that it was reasonable and necessary to provide technical assistance to counsel.
5. Counsel fees shall be based on the basis of:
   a) One senior and one junior counsel at the hearing;
   b) One senior and one junior counsel in conducting cross-examinations; and
   c) One senior counsel in defending cross-examinations.
6. Travel and accommodation expenses will be assessed on the basis of economy fares, except for overseas travel, and standard rooms in business class hotels based on single occupancy. Business class airfare shall be recoverable for overseas travel.
7. Photocopying costs will be assessed at $0.25 per page and the number of recoverable copies shall be limited to that which is reasonable and necessary.

8. Costs are recoverable for all other disbursements reasonably incurred (e.g., transcripts, translation services, computer searches).

"Michael D. Manson"
Judge

FEDERAL COURT

SOLICITORS OF RECORD

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