Federal Court  Cour fédérale

Date: 20130219

Docket: T-2021-10
Docket: T-833-11

Citation: 2013 FC 141

BETWEEN:

Docket: T-2021-10

TEVA CANADA LIMITED

Plaintiff
(Defendant by Counterclaim)

and

NOVARTIS AG

Defendant
(Plaintiff by Counterclaim)

Docket: T-833-11

BETWEEN:

APOTEX INC.

Plaintiff
(Defendant by Counterclaim)

and

NOVARTIS AG

Defendant
(Plaintiff by Counterclaim)

PUBLIC REASONS FOR JUDGMENT
(Confidential Reasons for Judgment issued February 8, 2013)

SNIDER J.

I. Introduction

A. *Overview*

[1] Novartis AG (Novartis) is the recorded owner of Canadian Patent No. 2,093,203 (the '203 Patent), a patent applied for on April 1, 1993, granted to Novartis on November 26, 2002, and which will expire on April 1, 2013. Novartis Pharmaceuticals Canada Inc. (Novartis Canada), a related corporate entity, sells a drug in Canada with the trademark of GLEEVEC, which is best known as a highly effective drug for the treatment of chronic myeloid leukemia (CML). The active ingredient in GLEEVEC is imatinib mesylate. Imatinib and its salt, imatinib mesylate, are compounds included in the '203 Patent.

[2] Teva Canada Limited (Teva) wishes to sell a generic version of imatinib. On December 3, 2010, Teva commenced an action against Novartis, seeking a declaration under s. 60(1) of the *Patent Act*, RSC 1985, c P-4 (*Patent Act*) that certain of the claims of the '203 Patent are invalid (the Teva Impeachment Action; Court File No. T-2021-10).

[3] Apotex Inc. (Apotex) also is planning to sell a generic version of imatinib. On May 13, 2011, Apotex commenced an action against Novartis, seeking a declaration under s. 60(1) of the *Patent Act* that the '203 Patent and each of its claims are invalid (the Apotex Impeachment Action; Court File No. T-833-11).

[4] Each of Teva and Apotex has also taken steps to obtain regulatory approval for the sale of imatinib. Specifically, each company has: (a) applied to the Minister of Health (the Minister) for a Notice of Compliance (NOC) in respect of orally administered 100 mg and 400 mg tablets containing imatinib, pursuant to the *Patented Medicines (Notice of Compliance) Regulations*, SOR/93-133 (the *PM (NOC) Regulations* or *Regulations*); and, (b) served Novartis Canada with a Notice of Allegation (NOA) with respect to the '203 Patent, in which Teva or Apotex, as applicable, alleges that all or certain claims of the '203 Patent are invalid.

[5] In response to each of the NOAs, Novartis Canada filed a Notice of Application requesting that the Court: (a) declare the NOA to be a nullity; or (b) issue an Order of Prohibition in accordance with s. 6(1) of the *PM (NOC) Regulations* preventing the Minister of Health from authorizing the second person to market imatinib until the expiry of the '203 Patent (the Teva Prohibition Application in Court File No. T-679-11 and the Apotex Prohibition Application in Court File No. T-599-11).

[6] Pursuant to the Order of Prothonotary Tabib dated May 30, 2011, the Teva Impeachment Action, the Apotex Impeachment Action, the Teva Prohibition Application and the Apotex Prohibition Application were consolidated. All four matters were dealt with in the course of 14 days of evidence and five days of argument.

[7] These Reasons for Judgment address the issues raised by the Teva and Apotex Impeachment Actions. In these reasons, Teva and Apotex are referred to as the Plaintiffs, except

where the context requires separate identification. The Prohibition Applications are jointly dealt within a separate set of Reasons for Judgment and Judgment:

(a) 2013 FC 142 (the Apotex Prohibition Application in Court File No. T-599-11); and

(b) 2013 FC 142 (the Teva Prohibition Application in Court file No. T-679-11.

B. *Summary of Issues and Conclusions*

[8] In bringing the impeachment actions, the Plaintiffs acknowledge that imatinib is an "extraordinary drug that offers extraordinary therapeutic benefits to those who are suffering from an insidious disease" (final written argument para 2). Neither of the Plaintiffs argues that imatinib, as of the relevant date, was not novel or was obvious. The arguments of the Plaintiffs rest primarily on their assertion that, as of April 1, 1993 (the Canadian filing date), the utility of imatinib and the other compounds of the '203 Patent had not been established. The Plaintiffs also assert that the '203 Patent fails to meet the disclosure requirements set out in s. 27(3) of the *Patent Act*.

[9] In its counterclaim, Novartis seeks a declaration that the '203 Patent is valid and asks that the Court order Apotex to deliver up all bulk imatinib in its possession.

[10] Thus, the key issues to be addressed are as follows:

1. Is the '203 Patent invalid because, as of April 1, 1993, the inventor, Dr. Jürg Zimmermann, had not satisfied the requirement that the compounds included in the claims of the '203 Patent have utility;

    - By demonstrating that the compounds would work as promised; or

    - On the basis that he could not soundly predict that the compounds would work as promised?

2. Does the specification of the '203 Patent "correctly and fully describe the invention and its operation or use as contemplated by the inventor", as required by s. 27(3) of the *Patent Act*?

3. If the '203 Patent is valid, do the quantities of bulk imatinib in the possession of Apotex infringe the '203 Patent; or, do these quantities fall with the regulatory or experimental use exemption of s. 55.2 (1) and (6) of the *Patent Act*?

[11] For the reasons set out in the following, I have concluded that:

1. As of April 1, 1993, the utility of Claims 5, 7, 29, 44 and 46 of the '203 Patent had been demonstrated or could soundly be predicted;

2. The '203 Patent meets the disclosure requirement of s. 27(3) of the *Patent Act*; and

3. Apotex need not deliver up the bulk imatinib in its possession.

II. Contents

[12] To assist the reader, I am including an outline of these reasons. The paragraph number for the beginning of each noted section is set out below:

III. Witnesses

[13] During the 14-day evidentiary phase of the trial, I heard from a number of fact and expert witnesses. Teva and Apotex jointly presented expert witnesses and presented individual fact witnesses. In the following, I will provide a brief overview of the expert and fact witnesses who appeared and the areas to which they testified. For the expert witnesses, I have set out a very short description of their education and experience in the areas for which this court found each of them to be qualified. More detailed references to the evidence of both fact and expert witnesses are contained in the appropriate sections of these reasons or, where necessary, in the reasons in the Prohibition Applications.

A. *Plaintiffs' Fact Witnesses*

[14] Teva presented Dr. Brian Des Islet, the Executive Director of Scientific Affairs at Teva, to testify on the actions of Teva (or its predecessor, ratiopharm) with respect to its abbreviated new drug submissions (ANDS) submitted to Health Canada and its decision to proceed with both an NOA under the *PM (NOC) Regulations* and the Teva Impeachment Action.

[15] Apotex put forward a number of fact witnesses. Dr. Bernard Sherman, the founder and current Chairman of Apotex, testified with respect to two different matters. First, he spoke on matters generally related to Apotex's corporate strategy and specifically concerning Apotex's decision to pursue both a NOA under the *PM (NOC) Regulations* and the Apotex Impeachment Action. Dr. Sherman also addressed the factual matters related to Apotex's claim of regulatory and experimental use exemptions to infringement.

[16] A number of other Apotex witnesses testified on the matters related to the experimental and regulatory exemption; they were:

- Mr. Donald Barber, Formulation Development Manager at Apotex;

- Ms. Galina Ayyoubi, Associate Director of Quality Assurance and Process in the Quality Assurance Department at Apotex;

- Mr. Gordon Fahner, Vice President of Business Operations and Finance at Apotex; and

- Ms. Bernice Tao, Director of Global Regulatory Operations at Apotex, responsible for regulatory filings in Canada, the United States, the European Union and Australia.

[17] The Plaintiffs jointly presented Ms. Anne Bowes, Director of the Office of Submissions and Intellectual Property within the Therapeutic Products Directorate of Health Canada to testify about Health Canada's regulatory requirements for drug approvals.

B. *Plaintiffs' Experts*

[18] Dr. Lars Rönnstrand, Professor of Molecular Medicine, Lund University, Sweden was retained by counsel for the Plaintiffs. He was qualified as an expert in the areas of:

- Protein kinases and their role in normal and abnormal cellular functioning;

- Protein kinase inhibitors as potential therapeutic agents to treat hyperproliferative diseases, including tumours; and

- The design, analysis and understanding of *in vitro* and *in vivo* assays used to evaluate protein kinase inhibitors as potential therapeutic agents to treat hyperproliferative diseases, including tumours.

[19] Dr. Rönnstrand opined on the utility of the invention disclosed by the '203 Patent, as well as whether utility could be soundly predicted. He reviewed the scientific literature as of the filing date with respect to the kinases described in the patent and whether or not there was a conclusive link to the pathologies noted in the specification. Dr. Rönnstrand also critiqued the tests disclosed in the '203 Patent as well as those later revealed by Novartis.

[20] Dr. Clayton Heathcock is a chemist with over 50 years of academic experience in organic chemistry and medicinal chemistry. He is currently Professor Emeritus at the University of California at Berkeley. From 2005 to 2008, he also held the position of Chief Scientist of the Berkeley branch of the California Institute for Quantitative Biosciences. Dr. Heathcock was qualified as an expert in synthetic organic chemistry and medicinal chemistry, including understanding and analyzing synthetic processes for making organic compounds intended to be used as pharmaceutical products and structure activity relationships (SARs) of organic compounds intended to be used as pharmaceutical products.

[21] Dr. Heathcock opined on the utility of the invention disclosed by the '203 Patent, as well as whether utility could be soundly predicted. In particular, Dr. Heathcock commented on the processes to prepare the claimed compounds as well as their structures and chemical properties.

C. *Novartis's Fact Witnesses*

[22] Novartis called three fact witnesses to speak to the discovery and development of the compounds of the '203 Patent at Ciba-Geigy Limited (Ciba-Geigy), predecessor in interest to Novartis.

[23] Dr. Nicholas Lydon, who holds a Ph.D. in biochemistry, worked at Ciba-Geigy from 1985 to 1997. During that time, he established the protein kinase research group at Ciba-Geigy. During his testimony, Dr. Lydon discussed the targets of the protein kinase group and how the group pursued its research goals. Dr. Lydon testified about decision-making processes designed to determine which molecules were assessed and promoted. He presented annual reports, progress reports and other documentation produced by the protein kinase group in the course of its work. He also explained the role of different individuals in the protein kinase group and how external collaborators, such as Dr. Brian Druker, became involved.

[24] Dr. Jürg Zimmermann, a medicinal chemist, is the inventor named in the '203 Patent. He described his role in the chemistry laboratory of the protein kinase group at Ciba-Geigy, explaining how molecules were made, screened, and optimized to be selective and potent inhibitors. Dr. Zimmermann discussed his path to the invention that became the subject of the '203 Patent.

[25] Dr. Doriano Fabbro joined Ciba-Geigy in 1991 and worked in the protein kinase group, developing assays and inhibitors relating to protein kinase C (PKC). Dr. Fabbro provided the

reasons why PKC was interesting to researchers in the context of cancer and multi-drug resistance at the filing date. He also explained some of the testing of the compounds of interest.

D. *Novartis's Experts*

[26] Dr. Richard Van Etten is the Chief of the Division of Hematology/Oncology and an attending physician on the bone marrow transplant and hematologic malignancies service and haematology/oncology consult service at Tufts Medical Centre, Boston Massachusetts. He is also the current Director of the Tufts Cancer Centre. In addition to being a practising physician, Dr. Van Etten holds a Ph.D. in Biophysics. Dr. Van Etten was qualified to give expert testimony as a medical doctor and a research scientist in the following areas:

- Mechanisms of cell growth and cell signalling, and the importance of tyrosine kinases in these cellular functions;

- Cancer cells, including the role of oncogenes and tumour suppressing genes in cancer cells;

- Protein kinases, including PKC, PDGF-R and ABL kinases, and their known association with certain cancers (including chronic myeloid leukemia (CML)) and other proliferative disorders as of April 1, 1993;

- Methods used for the treatment of cancer and theories relating to potentially new cancer treatments, including methods and theories relating to CML, as of April 1, 1993;

- The relevance of kinase selectivity in identifying compounds for the potential use as protein kinase inhibitors;

- *In vitro* tests used to identify compounds that may be effective as selective protein kinase inhibitors, including anti-proliferation, cell-free and whole cell tests that may be performed on various kinases;

- The use of *in vivo* testing used to evaluate the efficacy of protein kinase inhibitors; and

- Gleevec and its impact on the prognosis of patients diagnosed with CML.

[27] Dr. Van Etten reviewed the '203 Patent and opined on the patent's promise and the utility of the patent claims. He summarized the state of the art with respect to PKC, PDGF-R and ABL kinases at the filing date and the extent to which these kinases were implicated in cancer pathology. He commented on the testing performed by Novartis, what conclusions may be drawn from that testing and which testing methods were available at the filing date.

[28] Dr. James Wuest, who holds a Ph.D. in organic chemistry, is a Professor of Chemistry at Université de Montréal. Dr. Wuest was qualified to give opinion evidence with respect to synthetic organic chemistry, including SAR analyses and extrapolation of these SAR analyses to medicinal chemistry issues.

[29] Dr. Wuest testified about the organic chemistry and utility of the process Claim 44 and the compound claims. He described the three different processes encompassed by Claim 44 and the extent to which these processes and the reactions inherent in them were known at the time of filing. Dr. Wuest opined on the compounds made and tested by Novartis, and whether they were representative of particular claims, focussing on Claim 7 read with Claim 5.

[30] Dr. Carl-Henrik Heldin is the Director of the Ludwig Institute for Cancer Research in Uppsala, Sweden. Dr. Heldin was qualified to give opinion evidence relating to:

- Protein kinases and their role in normal and abnormal cellular functioning;

- Protein kinase inhibitors, including as potential therapeutic agents, for the use in disorders associated with kinase dysregulation, including tumours and atherosclerosis; and

- Design and analysis of *in vitro* and *in vivo* experiments used to evaluate protein kinase inhibitors including as potential therapeutic agents for use in disorders associated with kinase dysregulation, such as tumours and atherosclerosis.

[31] Dr. Heldin testified about the state of art in 1993, the studies conducted by Novartis and whether the invention disclosed in the patent had utility. Dr. Heldin explained the tests performed on various compounds of formula I and what conclusions may be drawn from those results. Dr. Heldin focussed on Claim 29, Claim 46 dependent on Claim 29 and Claim 7 dependent on Claim 5.

E. *Complaints by the Plaintiffs about Drs. Heldin and Van Etten*

[32] The Plaintiffs, in final argument, were generally critical of the testimony of Drs. Van Etten and Heldin and requested that I give diminished weight to their evidence. I do not agree that the evidence of these experts is tainted as posited by the Plaintiffs. The criticisms relate to small portions of the evidence and do not affect the great assistance that both experts provided during this trial to my understanding of the subject matter of the '203 Patent.

[33] With respect to Dr. Van Etten, the main complaint of the Plaintiffs is that he did not construe the patent through the eyes of a person of ordinary skill in the art; rather, they submit that he reviewed everything as a "stone cold expert" in the field. In support for this position, they refer to the following exchange (9T1741-1742) where I had engaged Dr. Van Etten in a discussion of the person of ordinary skill in the art:

> MADAM JUSTICE SNIDER: During your testimony, you referred a lot to what you had done and the state of the art in 1993, and you were fortunate enough to be very active in that area. Would you consider yourself to be a person of ordinary skill in the art?
>
> THE WITNESS: I'm not sure what that actually means in the legal sense. I consider myself, if I can use the slang, to be a stone cold

> expert in this whole area. My entire career depended on it. I was right in the middle, in the thick of all of this, in this particular area around ABL and inhibitors and mouse models, so I think I'm pretty knowledgeable.

[34] I am not sure what a "stone cold expert" is. I assume that Dr. Van Etten was telling me that he had much more expertise than the "ordinary" skilled person. And, of course, in assisting the court, a "stone cold expert" is necessary to deal with the complex scientific concepts involved. However, I do not, as do the Plaintiffs, take this to be an admission that Dr. Van Etten did not provide me with his opinion of what a person of ordinary skill in the art would have known as of the relevant date.

[35] Dr. Van Etten did make some references to his understanding of the state of the art as of April 1, 1993 which raise a little concern. Specifically, in response to a question during examination in chief, Dr. Van Etten stated (8T1554) that he was asked "if a person skilled in the art such as myself could have a reasonable inference as to the utility" (emphasis added). Later in the same examination, Dr. Van Etten stated (8T1555) that "It's really about whether an expert in cancer biology at the time would have been able to reasonably infer, given the evidence, that PDGF and it's receptor were involved in certain types of cancer" (emphasis added). These comments must be read in context. Having read the transcript in its entirety and his report, I am satisfied that, despite the first statement, Dr. Van Etten was well aware of the task of patent construction and the difference between an expert such as himself and the person of ordinary skill in the art. With respect to the second comment about the "expert in cancer biology", I observe that the notional skilled person, in this case and as discussed below, will have

considerable expertise in medicinal chemistry. A person with such expertise may well be referred to as an "expert".

[36] The other reason provided by the Plaintiffs is that Dr. Van Etten acted as an advocate for Novartis contrary to the role of an expert and contrary to the declaration made in accordance with Rule 52.2(1)(c) of the *Federal Courts Rules,* SOR/98-106. This submission is often made by a party when an expert provides an opinion that does not agree with its expert or its position on the evidence. The argument may, in some cases, have substance. In this case, it does not. Dr. Van Etten, even in the examples cited by the Plaintiffs, was responding honestly and openly to questions posed to him. He did not blindly adhere to an opinion without merit. Rather than advocating for Novartis, I saw Dr. Van Etten as an advocate for his expert opinion; I see no problem with such advocacy.

[37] In addition to arguing that Dr. Heldin was an advocate for Novartis – an argument that I reject for the same reasons as expressed with respect to Dr. Van Etten – the Plaintiffs submit that Dr. Heldin provided his opinion without seeing or requesting to see all of the relevant documents.

[38] It is true that Dr. Heldin was not provided with Novartis Production Document 250 (ND250), which describes an experiment conducted by the Ciba-Geigy researchers. Maybe he should have been given this document – particularly since it was referred to by Dr. Rönnstrand in his report. However, in my opinion, this oversight is not sufficient reason to discount the entire testimony of Dr. Heldin. The alleged importance of ND250, and the results of a "failed"

experiment on one of the compounds of the '203 Patent, is much exaggerated. The mere fact that Dr. Rönnstrand felt that this experiment was relevant does not necessarily make it so. This question is discussed in greater detail below.

[39] A similar argument is made by the Plaintiffs about certain summary internal Ciba-Geigy reports (ND151 and ND153) that were not provided to Dr. Heldin. Both of these reports were prepared after April 1, 1993. It is not at all strange that they were not provided to Dr. Heldin for preparation of his expert report where he was asked to form opinions as of April 1, 1993.

[40] In any event, during his oral testimony, Dr. Heldin provided clear responses to the questions posed to him on the "missing documents".

[41] I am not prepared to discount the helpful opinions of Dr. Heldin on all issues because he was not given three documents which are of questionable relevance to the issues before me.

[42] The Plaintiffs assert that the testimony of Drs. Van Etten and Heldin is similar to that of Dr. Bartlett, whose testimony was assigned less weight in *Sanofi-Aventis Canada Inc v Apotex Inc*, 2009 FC 676 at paras 126-131, 77 CPR (4th) 99 [*Ramipril I (FC)*], aff'd 2011 FCA 300, 97 CPR (4th) 415 (15T2881-2886). Although some of the statements by Novartis's experts in this case may be superficially similar to Dr. Bartlett's, the context in which these opinions were presented demonstrates that *Ramipril I (FC)* and Dr. Bartlett's evidence presented very different circumstances.

[43] In *Ramipri I (FC)*, the patent, the expert evidence, the relevant knowledge of the skilled person and the factual circumstances were very different. On this basis alone, it is difficult to compare Dr. Bartlett's testimony to that of Dr. Van Etten and Dr. Heldin in a meaningful way. For example, the history of ACE inhibitors and their clinical use was significant at the time the inventors filed the ramipril patent (*Ramipril I (FC)*, above at paras 53-62). By contrast, the use of selective protein kinase inhibitors to treat hyperproliferative disorders was in its infancy at the filing date of the '203 Patent.

[44] Further, the concern with Dr. Bartlett's testimony in *Ramipril* was not confined to his interpretive approach to the promise of the patent; another significant problem that troubled the Court in *Ramipril I (FC)* was Dr. Bartlett's inconsistent testimony in the *Ramipril* trial as compared to his evidence in *Laboratoires Servier v Apotex Inc*, 2008 FC 825, 67 CPR (4th) 241 [*Perindopril*], aff'd 2009 FCA 222, 75 CPR (4th) 443. In the *Perindopril* trial, Dr. Bartlett opined that other patents in the field promised both an anti-hypertensive effect as well as ACE inhibition, while in the *Ramipril* trial, Dr. Bartlett significantly qualified this statement, referring to potential ACE inhibition only (*Ramipril I (FC)*, above at paras 129-130). This significant discrepancy was an important reason why the Court questioned Dr. Bartlett's objectiveness and gave his evidence less weight. The Plaintiffs have not demonstrated any reason rising to this level of significance why Dr. Van Etten and Dr. Heldin did not testify objectively.

IV. Background to the '203 Patent

[45] The '203 Patent and this trial involved a considerable amount of evidence related to medicinal chemistry and other branches of related science. In this section of the reasons, I have attempted to provide a brief overview of the complex scientific concepts involved and the history of the '203 Patent.

[46] This case requires some knowledge of certain human genes and protein kinases. I adopt the Human Genome Organisation (HUGO) nomenclature used in the scientific community to refer to genes and proteins, as explained by Dr. Van Etten and Dr. Rönnstrand. Names of human genes are capitalized and italicized, while names of proteins are capitalized but not italicized.

[47] Key concepts relate to certain protein kinases and the ways in which they may be uncoupled from the systems that regulate them, leading to diseases of uncontrolled cell division such as cancer. All of the experts who testified were extremely helpful in establishing a base level of information and knowledge around which I could frame this decision. At this stage, there was no disagreement among the experts.

A. *Protein Kinases*

(1) Protein Kinases, Cell Signalling and Cell Proliferation

[48] Enzymes catalyze chemical reactions between particular molecules, facilitating these reactions and allowing them to proceed. Protein kinases catalyze the covalent attachment of a phosphate group from ATP to a protein, a reaction known as phosphorylation. Kinases may be located in the interior of the cell in the cytosol or they may span the cell membrane. There are two groups of kinases of interest in these actions:

- One group of kinases, including PKC, phosphorylate serine and threonine amino acids.

- A second group of kinases, including platelet-derived growth factor receptor kinase (PDGF-R kinase) and Abelson kinase (ABL kinase), phosphorylate tyrosine amino acids.

[49] Protein kinases play an important role in cell signalling through appropriate regulation of their activity. Kinases are generally present in a cell in their inactive state and have low levels of catalytic activity. However, they may become active upon receiving a particular signal, which causes them to phosphorylate other proteins, changing the behaviour of these phosphorylated proteins. These proteins may interact differently with other proteins, relocate to another part of

the cell or, if the phosphorylated protein is itself an enzyme, its catalytic activity may increase or decrease.

[50] The response of a protein kinase to a stimulus may lead to changes in the cell as a whole through a signalling cascade. The signal that a kinase transmits through phosphorylation of a protein may be relayed from one molecule to another in a linear fashion or a branching fashion, allowing for regulation of multiple cellular processes. For example, when PDGF-R kinase is activated by a growth factor, it can phosphorylate proteins in the RAS family. RAS proteins activate a serine/threonine kinase called RAF, which activates another kinase called MEK, which in turn will activate MAP kinase. MAP kinase will activate a number of proteins, including transcription factors, which bind to particular regions of DNA and affect the expression of certain genes, such as *c-FOS*.

[51] Cell signalling initiated by protein kinases may eventually lead to changes in overall cell behaviour. For example, cells may mature into a specialized cell type, a process known as differentiation. They may also divide, a process referred to as cell proliferation. Protein kinases may also promote attachment or detachment of the cell to its surrounding environment as well as cell survival or cell death.

[52] Genes encoding proteins involved in cell signalling, including tyrosine kinases, may become mutated, leading to dysregulation of cell proliferation and associated diseases. In the context of cancer, oncogenes cause cells to behave in ways that are similar to cancer cells, often because they produce signalling proteins that have increased activity.

(2) ABL Kinase and Chronic Myeloid Leukemia

[53] ABL kinase is a tyrosine kinase located in the cytosol. ABL kinase plays a role in cell signalling and is expressed in many cells of the body. The gene encoding this kinase, known as c-*ABL*, is located on chromosome 9. A similar gene to c-*ABL*, known as v-*ABL*, is the oncogene contained in the Abelson murine leukemia virus that causes mice to suffer from leukemia.

[54] A mutated form of c-*ABL*, known as *BCR-ABL*, is linked to a human form of cancer known as chronic myeloid leukemia or CML. CML is a form of cancer characterized by excessive proliferation of neutrophils, cells in the body that form part of the immune response, as well as their precursors. As the disease progresses, these cells accumulate in the blood and in the spleen. Eventually, a patient's normal mature blood cell production becomes affected which eventually causes death.

[55] As of April 1, 1993, there were three possible treatments for CML:

- Myelosuppressive drugs which could interfere with the proliferation of blood cells in the bone marrow, offering, however, little beyond palliative therapy;

- Interferon-alfa, to which few patients responded and which was highly toxic; and

- Stem cell transplantation, which was successful in only 65% of patients and which, due to its toxicity, was not available to many patients.

[56] There is a well-established connection between BCR-ABL kinase and CML. In 1960, Nowell and Hungerford observed that CML patients possessed a particularly small version of chromosome 22, known as the Philadelphia chromosome (Ph chromosome) (PC Nowell and PA Hungerford, "A minute chromosome in human chronic granulocytic leukemia", 132 Science 1497). It was later discovered that the Ph chromosome is created from an exchange of genetic material between chromosomes 9 and 22, which forms the fusion gene, *BCR-ABL*. This fusion gene codes for the fusion protein, BCR-ABL. Researchers discovered that BCR-ABL is a tyrosine kinase that is constitutively active, meaning that it has abnormally high activity compared to the normal ABL kinase.

[57] The relationship of BCR-ABL to CML is important in the context of imatinib and this trial. A more detailed description of this link and the other literature and knowledge in the public domain up to the filing of the '203 Patent is found later in these reasons.

(3) PDGF-R Kinase

[58] PDGF-R kinase is a transmembrane tyrosine kinase that is mainly found in connective tissue cells such as fibroblasts, smooth muscle cells, pericytes close to the capillaries and the glial cells of the nervous system. When platelet derived growth factor (PDGF) binds to the extracellular receptor on PDGF-R, this leads to the formation of a signalling complex; two adjacent PDGF-R molecules come together, they phosphorylate each other and they both become activated. This creates sites where other signalling proteins may attach.

[59] Researchers had investigated the connection between PDGF-R and cancer, as well as PDGF-R and atherosclerosis prior to April 1, 1993, as explained in further detail later in these reasons.

(4) PKC

[60] PKC is a family of serine/threonine kinases, comprised of a number of PKC isozymes. These kinases are located in the cytosol of almost every cell in the body, where they regulate many processes including cell proliferation and survival. There are three distinct subgroups of PKC isozymes, which differ based on what substances they require for activation and in their biological activity. As of April 1, 1993, researchers had investigated the link between PKC and cancer, as well as PKC and multi-drug resistance.

B. *Selective Kinase Inhibitors*

[61] The essence of the '203 Patent is selective inhibition of particular protein kinases. If the activity of a protein kinase is somehow "blocked" by a compound, referred to as an inhibitor, the protein kinase cannot transmit signals to the nucleus of the cell to cause cell growth and proliferation.

[62] If a kinase inhibitor interferes with several protein kinases, it would disrupt many normal physiological processes. This in turn would cause unnecessary and unwanted side effects and

toxicity. However, if a kinase inhibitor is selective for one kinase or a small subset of kinases, it would be a much better drug candidate with the potential for treatment.

C. *The Protein Kinase Group at Ciba-Geigy*

[63] The compounds of the '203 Patent were developed in the laboratories of Ciba-Geigy. Three witnesses who were important players in the development of the compounds of the '203 Patent at Ciba-Geigy testified in this trial - Dr. Lydon, Dr. Fabbro and the named inventor, Dr. Zimmermann. Each is an impressive scientist who testified in a straight-forward, credible manner.

[64] Dr. Lydon told the story of how, in 1985, he and Dr. Alex Matter started the protein kinase group (referred to as the PK Group) at Ciba-Geigy. This group focussed on the role of protein kinases, the "molecular switches" of cell signalling, and the development of inhibitors to treat diseases when these "switches" became dysregulated (10T1956). A group of researchers worked on PKC and another group worked on four tyrosine kinases of interest: epidermal growth factor receptor (EGF-R) kinase, c-erb B2 kinase, PDGF-R kinase and ABL kinase. Much of the early work was done to establish the project, including the development of tools and assays as well as the isolation of target enzymes. Once this was accomplished, the focus of the project became the synthesis of reference compounds, identification of lead molecules which had activity against the target enzymes and optimization of these molecules to improve selectivity and potency as well as physical and chemical properties.

[65] Dr. Zimmermann, the named inventor of the '203 Patent and a medicinal chemist, began his work on the protein kinase project as an investigator in the PK Group (12T2272-2274, 2287-2290). He told the story of the development of the claimed compounds from certain starting compounds.

[66] The PK Group began with a number of reference compounds, which became the "starting point" for their research (12T2288). Of critical importance, a compound known as staurosporine came to the attention of the group in 1986. As described by Dr. Fabbro (12T2459), the interest in this compound came from its properties as a protein kinase inhibitor; unfortunately, staurosporine was not selective. The chemists at Ciba-Geigy modified the structure of the molecule to increase potency and selectivity. These modifications led to the compounds that became the subject matter of the '203 Patent.

[67] In April 1992, when the PK Group had developed inhibitors of PKC, they decided to file a patent (12T2306-2308). This patent relating to the PKC inhibitors was filed in Switzerland and it is the priority application to which the '203 Patent refers.

[68] Two important discoveries occurred in the year between the filing of the priority application and the Canadian patent. The first important breakthrough occurred when the chemists created molecules that could inhibit PDGF-R kinase and ABL kinase in addition to PKC (12T2290-2293). These compounds contained an NHCO phenyl group, which led to activity against these two additional kinases. A second important discovery was the creation of a molecule selective for PDGF-R and ABL kinase, which did not inhibit PKC (12T2293-2308).

These molecules contained a "flag methyl group" (12T2294) which accounted for their selectivity. The PK Group continued to optimize this new class of inhibitors, adding a piperazine group to improve solubility.

[69] On April 1, 1993, the PK Group filed a patent application in Canada; this became the '203 Patent issued November 26, 2002 . In this patent application, and in others filed around this time in other countries, Dr. Zimmermann referred to the PKC inhibitors as well as the activity of the new compounds against ABL kinase and PDGF-R kinase (12T2308-2309).

[70] After April 1, 1993, Ciba-Geigy proceeded to focus primarily on the compounds that came to be known as the Group 2 compounds. Over the next year, further testing demonstrated that CGP 57148 was the molecule of greatest interest. CGP 57148 – now known as imatinib – entered clinical trials in 1998 (Van Etten Report, TX 37 at para 156). Imatinib was eventually granted an NOC/c by Health Canada, which allows for promising, breakthrough therapies to be approved quickly (Anne Bowes, 2AT238-243).

[71] Imatinib has revolutionized the treatment of CML. Before imatinib became available, patients receiving the best available treatment had a mean survival rate ranging from 42 to 98 months. However, once imatinib entered the market, "[w]hat once was a death sentence has now become a manageable chronic illness with overall survival rates equal to the general population" (Van Etten Report, TX 37, paras 155-157). It is not an exaggeration to say that the work done by the Ciba-Geigy scientists changed the lives of patients living with CML; with imatinib, such

patients can lead almost normal lives while living with a disease that would otherwise have been a death sentence.

V. Burden

[72] In these proceedings, the Plaintiffs bear the burden of establishing, on a balance of probabilities, any facts which render the '203 Patent invalid, keeping in mind the presumption of validity (*Eli Lilly and Co v Apotex Inc*, 2009 FC 991 at paras 348-349, 370, 80 CPR (4th) 1 [*Cefaclor*], aff'd 2010 FCA 240, 90 CPR (4th) 327). Upon the issuance of a patent, the patent as a whole is presumed to be valid, absent evidence to the contrary (Section 43(2) of the *Patent Act*; see for example *Abbott Laboratories v Canada (Minister of Health)*, 2007 FC 455 at para 90, [2008] 2 FCR 636, aff'd 2008 FCA 44, 68 CPR (4th) 167; *Windsurfing Int'l Inc v Entreprises Hermano Ltée* (1982), 69 CPR (2d) 176 at 181-182, [1982] FCJ No 1144 (TD)). Once the party attacking the patent has adduced evidence to rebut the presumption, the Court must evaluate the evidence on a balance of probabilities (*Rubbermaid (Canada) Ltd v Tucker Plastic Products Ltd* (1972), 8 CPR (2d) 6 at 13-14, [1972] FCJ No 1003 (TD)).

VI. Claims Construction

A. *Principles of Claims Construction*

[73] The first step in a patent suit is to construe the claims, in accordance with principles that are well established in the jurisprudence (see, for example, *Whirlpool Corp v Camco Inc*, 2000

SCC 67, [2000] 2 S.C.R. 1067 [*Whirlpool*]). This jurisprudence teaches that claims are to be interpreted in a purposive way 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 at para 49, 54 CPR (4th) 435 [*Dimplex*], aff'd 2007 FCA 278, 60 CPR (4th) 277). As cautioned, over and over, by the jurisprudence, construction of the claims must be approached with a mind willing to understand. For example, Justice Binnie in *Whirlpool*, above at paragraph 49(c) stated the following:

> The orthodox rule is that a patent "must be read by a mind willing to understand, not by a mind desirous of misunderstanding", *per* Chitty J. in *Lister v. Norton Brothers and Co.* (1886), 3 R.P.C. 199 (Ch. D.) at p. 203. A "mind willing to understand" necessarily pays close attention to the purpose and intent of the author.

[74] Similar caution can be seen in the comments of Justice Dickson in *Consolboard Inc v MacMillan Bloedel (Sask.) Ltd*, [1981] 1 SCR 504 at 520, 122 DLR (3d) 203 [*Consolboard*]:

> There is no occasion for being too astute or technical in the matter of objections to either title or specification for, as Duff C.J.C. said, giving the judgment of the Court in *Western Electric Company, Incorporated, and Northern Electric Company v. Baldwin International Radio of Canada*, [[1934] S.C.R. 570], at p. 574, "where the language of the specification, upon a reasonable view of it, can be so read as to afford the inventor protection for that which he has actually in good faith invented, the court, as a rule, will endeavour to give effect to that construction". Sir George Jessel spoke to like effect at a much earlier date in *Hinks & Son v. Safety Lighting Company*, [(1876), 4 Ch. D. 607]. He said the patent should be approached "with a judicial anxiety to support a really useful invention". [Emphasis added.]

[75] Construction of the claims is a matter for the court to decide. The court is called on to determine, on an objective basis, what a hypothetical skilled person would have understood the claims to mean (*Whirlpool*, above at paras 45, 53). Where a patent is of a highly technical nature,

the person skilled in the art will be someone possessing a high degree of expert scientific knowledge in the particular field of art to which the patent relates (*Aventis Pharma Inc v Apotex Inc*, 2005 FC 1283 at para 64, 278 FTR 1 [*Ramipril II (FC)*]; *Apotex Inc v Syntex Pharmaceuticals International Ltd et al* (1999), 166 FTR 161 at para 38, [1999] FCJ No 548 (TD)).

[76] I wish to emphasize that the claims – and not the disclosure – are the essence of a patent and it is the claims that must be interpreted. While the specification, as a whole, will describe the invention, the scope of the monopoly is defined by the claims (see *Amfac Foods Inc v Irving Pulp & Paper, Ltd* (1986), 12 CPR (3d) 193 at 198, 72 NR 290 (FCA); *CH Boehringer Sohn v Bell-Craig Ltd* (1962), 39 CPR 201 at 243, 1962 Ex CR 201, aff'd [1963] SCR 410, 41 DLR (2d) 611). As stated by Justice Binnie in *Whirlpool*, above at paragraph 45:

> The key to purposive construction is therefore the identification by the court, with the assistance of the skilled reader, of the particular words or phrases in the claims that describe what the inventor considered to be the "essential" elements of his invention. [Emphasis added.]

[77] However, where necessary, the court may have resort to the disclosure to assist in the exercise (*Eli Lilly Canada Inc v Apotex Inc*, 2008 FC 142 at para 25, 63 CPR (4th) 406, aff'd 2009 FCA 97, 78 CPR (4th) 388; *Eli Lilly Canada Inc. v. Novopharm Ltd.*, 2007 FC 596 at para 103, 58 CPR (4th) 214). Stated differently, the Court should construe the claims in light of the description in the specification, assisted by experts as to the meaning of technical terms if such terms cannot be understood by the Court from reading the specification (*Shire Biochem Inc v Canada (Minister of Health)*, 2008 FC 538 at para 22, 328 FTR 123; *Whirlpool*, above at para 45).

[78] With these overarching principles in mind, I turn to the patent in question.

B. *The hypothetical skilled person*

[79] As noted, claims must be construed from the view of a hypothetical skilled person. Thus, as a preliminary matter, I must define what attributes would be held by our hypothetical skilled person or person of ordinary skill in the art.

[80] Apotex submits that I should accept the description of Dr. Rönnstrand, from his expert report (TX 13, para 19), to define our skilled person:

> [T]he 203 Patent is addressed to persons having a graduate level degree in pharmacology, biology, biochemistry, medicinal chemistry, organic chemistry, pharmaceutical sciences, or a closely related field. These persons would also have at least two to three years of experience in applications related to the development of therapies for the treatment of conditions or diseases, for example tumours, that respond to inhibition of protein kinases, including experience employing various *in vitro* and *in vivo* assays.

[81] Novartis does not disagree but notes the emphasis placed on the knowledge of organic and medicinal chemistry by Dr. Wuest in his report (TX 53, para 17).

[82] As is often the case, the notional skilled person will likely consist of a team of people with a combination of the skills identified by the experts. Moreover, although the person of ordinary skill in the art will not be an "expert", in the sense used by the Court, the '203 Patent requires a person with considerable expertise in the areas of organic and medicinal chemistry, as

also noted by Dr. Heathcock (T938; Heathcock Report, TX 22, para 23), as well as Dr. Heldin (T2624; Heldin Report, TX 71, para 27).

C. *The Patent Specification*

[83] A patent normally consists of two separate sections – the disclosure or description of the invention followed by the claims. Together, the disclosure and the claims make up the specification of the patent (see *Consolboard*, above at 520).

[84] Even though the task at hand is to construe the claims of the '203 Patent, I begin with a study of the '203 Patent disclosure. This study will help situate not only the proper construction of the claims but will assist in the later discussion of: (a) the utility of the claims where the "promise" of the patent will need to be ascertained; and (b) the sufficiency of the '203 Patent where the nature of the invention must be determined.

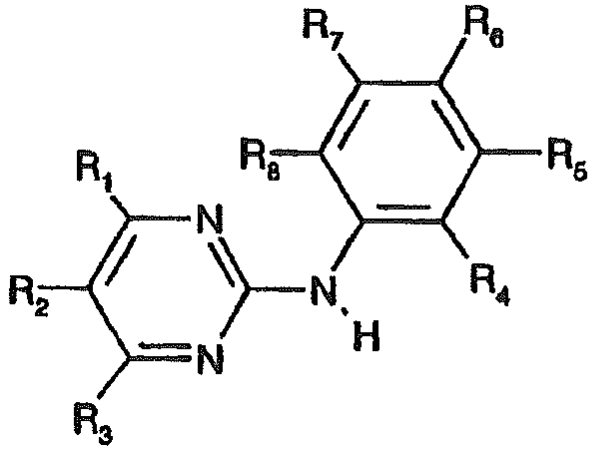
[85] The importance of the chemistry component of the '203 Patent is reflected in its title, "PYRIMIDINE DERIVATIVES AND PROCESSES FOR THE PREPARATION THEREOF". The first paragraph of the disclosure is far more descriptive:

> The invention relates to N-phenyl-2-pyrimidine-amine derivatives, to processes for the preparation thereof, to medicaments comprising those compounds, and to the use thereof in the preparation of pharmaceutical compositions for the therapeutic treatment of warm-blooded animals.

[86] This four-fold description is reflected in the claims where:

- Claims 1 to 39 are claims to compounds;
- Claims 40 to 43 are claims to "pharmaceutical compositions" (medicaments);
- Claim 44 is a claim to the process for making the claimed compounds; and
- Claims 45 to 48 claim particular uses of the compounds.

[87] Following these introductory comments, the patent sets out the chemical structure of formula I compounds:



(I),

[88] The following four pages of the patent describe the various possible substituents for R_1 to R_8.

[89] At page 5 of the disclosure, the patent begins to describe and delineate the invention, beginning with the important therapeutic use to which the compounds may be put:

> The compounds of formula I have valuable pharmacological properties and can be used, for example, as anti-tumoral drugs and drugs against atherosclerosis.

[90] An overview of the knowledge in the field is then set out describing the operation of phosphorylation of proteins and the role of kinases. Kinases of particular relevance are "the serine/threonine kinases [including] protein kinase C and the tyrosine kinases [including] the PDGF (platelet-derived growth factor)-receptor tyrosine kinase". These particular enzymes are referred to as PKC and PDGF-R.

[91] The disclosure then turns to a more detailed description of the compounds, beginning with a subset of formula I compounds referred to at trial (although not in the '203 Patent) as the Group 1 compounds. As set out in the disclosure (sixth full paragraph, p. 5), "[t]he compounds of formula I wherein R_4 and R_8 are hydrogen selectively inhibit the enzyme [PKC]" (emphasis added).

[92] This is the first use in the '203 Patent of the terms "selectively" and "inhibit", terms which would have been well known to persons of ordinary skill in the art.

[93] The following several paragraphs of the disclosure (from page 5 to 7) appear to relate exclusively to the Group 1 compounds (from page 5 to 7). Some expansion of the notion of selective inhibition and potential use of the Group 1 compounds because of the function of PKC, the enzyme that they selectively inhibit, is provided.

[94] The inventor first explains the *in vitro* testing of the Group 1 compounds using PKC from pig brain. No specific compounds are mentioned although it is reasonable to assume that the illustrative Group 1 examples at pages 25 to 35 were those compounds tested (Dr. Rönnstrand, 4T733-734). The testing results are given as a range of IC_{50} values. There was inhibition of PKC "at a concentration of IC_{50} of as low as approximately from 0.1 to 10 µmol/litre, especially approximately from 0.05 to 5 µmol/litre". With respect to the inhibition of other enzymes (with some examples disclosed), the compounds inhibited those other enzymes "only at a far higher concentration, for example 100 times higher". This difference, in the statement of the inventor, "is an indication of the selectivity of the compounds of formula I".

[95] In the following paragraph the inventor ascribes certain properties to the Group 1 compounds, which properties flow from the inhibiting activity of the compounds:

> Owing to their inhibiting activity towards [PKC], the [Group 1 compounds] . . . can be used as tumour-inhibiting, immunomodulating and anti-bacterial active ingredients and, further, as drugs against atherosclerosis, the immunodeficiency disorder AIDS, and diseases of the cardiovascular system and the central nervous system. [Emphasis added.]

[96] In the third full paragraph at page 6, further testing is described. The inventor describes the test carried out to assess the inhibiting action of the Group 1 compounds on the growth of human T24 bladder carcinoma cells. Using the testing methodology described in the disclosure, the inventor reports that the IC_{50} values determined are "from 0.1 to 10 µmol/litre". Again, the patent provides only a range of IC_{50} values.

[97] This section of the disclosure is completed with another paragraph extolling the therapeutic possibilities for the Group 1 compounds, which flow again from their inhibitory properties:

> Owing to the properties described, the [Group 1 compounds] can be used especially as tumour-inhibiting active ingredients, for example for the treatment of tumours of the bladder. In addition, they are suitable for the further applications mentioned above for [PKC]-modulators and can be used especially in the treatment of diseases that respond to inhibition of [PKC]. [Emphasis added.]

[98] The disclosure then turns its attention to two further subsets of formula I; these compounds are referred to in the trial (although not in the patent) as Group 1A and Group 2 compounds. In a somewhat muddy single paragraph, the inventor sets out the following descriptions of the two subsets:

> Some of the compounds of formula I wherein R_4 and R_8 are hydrogen inhibit not only [PKC] but, at a concentration IC_{50} as low as approximately 0.01 to 5 µmol/litre, especially approximately from 0.05 to 1 µmol/litre, also certain tyrosine kinases, such as especially PDGF-receptor kinase or abl-kinase, for example v-abl-kinase. Compounds of formula I wherein at least one of the radicals R_4 and R_8 is other than hydrogen and is, for example, lower alkyl, such as methyl, are especially selective for the above-mentioned PDGF-receptor and abl-tyrosine kinases and inhibit [PKC] virtually not at all.

[99] The first sentence of this paragraph describes the Group 1A compounds. These compounds are said to inhibit PKC, as well as PDGF-R or v-ABL kinases. The inhibition is apparently evidenced from the range of IC_{50} values provided. Although unstated, the experts appeared to agree that the range set out applied to both PDGF-R and ABL inhibition for the Group 1A compounds.

[100] The second sentence of this paragraph is the first description of the compounds that became, in the years subsequent to the filing of the '203 Patent application, the most valuable compounds of the patent. These compounds were referred to during the trial as the Group 2 compounds, one of which is imatinib. According to the patent disclosure, the Group 2 compounds inhibit PDGF-R and ABL kinases but do not inhibit PKC. The key construction issue raised by the wording of this paragraph is whether the inventor is telling us that the inhibition of both PDGF-R and ABL are disclosed (the Plaintiffs' position) or that the inhibition of either PDGF-R or ABL is disclosed (Novartis's position). This issue is discussed below.

[101] This paragraph is followed with a short description of the role of PDGF in "normal growth and pathological cell proliferation, such as in carcinogenesis and disorders of the smooth muscle cells of blood vessels, for example in atherosclerosis and thrombosis".

[102] At page 8 of the patent, the first full paragraph describes three types of testing to determine the PDGF-R inhibition characteristics of certain of the formula I compounds. Although the paragraph does not set out which of the particular subsets of compounds were tested in which experiments, Dr. Rönnstrand agreed that the compounds tested were those outlined in the examples (4T733-734). The three types of tests were as follows:

1. The cell free inhibition of PDGF-R kinase activity *in vitro* "is measured in PDGF receptor immunocomplexes of BALB/c 3T3 cells", using known methods. The disclosure observes that "the compounds of formula I described in detail above [presumably, the Group 2 compounds although this is not expressly set out]

exhibit "PDGF-dependent cell-free receptor phosphorylation at concentrations of from 0.005 to 5 µmol/litre, especially from 0.01 to 1.0, more especially from 0.01 to 0.1 µmol/litre."

2. The next portion of the paragraph describes a method of detecting inhibition of PDGF-R in the intact cell through the use of the Western Blot Analysis. The formula I compounds "described in detail above" inhibit the tyrosine kinase activity of the PDGF receptor at concentrations of from 0.005 to 5 µmol/litre, especially from 0.01 to 1.0 and more especially from 0.01 to 0.1 µmol/litre".

3. Lastly, the disclosure states that "[a]t concentrations below 1.0 µmol/litre, these compounds also inhibit the cell growth of a PDGF-dependent cell line, namely BALB/c 3T3 mouse fibroblasts".

[103] The next paragraph contains the only specific mention of testing of inhibition of v-ABL kinase. It states that:

> The above-mentioned inhibition of v-abl-tyrosine kinase is determined in accordance with the methods of N. Lydon et al . . . and J.F. Geissler et al . . . In those methods [Val ^{5}]-angiotensin II and [γ-^{32}P] ATP are used as substrates.

[104] No results are provided in this paragraph. The statement is simply made that the "above-mentioned inhibition" of v-ABL kinase is determined in accordance with methods contained in published literature and names the compounds used as substrates. This gives rise to an area of disagreement between the parties. Novartis submits that this paragraph should be read

as including the test results set out in the earlier paragraph; the Plaintiffs argue that no test results are provided for the inhibitory ability of the Group 2 compounds against v-ABL kinase. Although this issue is not directly relevant to claims construction, it is relevant to the issue of sufficiency of disclosure. I address this issue below.

[105] Finally (p. 8, third and fourth full paragraphs), the patent sets out that:

> Owing to the properties described, compounds of formula I can be used not only as tumour-inhibiting active ingredients but also as drugs against non-malignant proliferative diseases . . . [Emphasis added.]

[106] The experts agree that this paragraph likely is a reference to just the Group 2 compounds (see for example, Dr. Rönnstrand's direct examination, 3T437-438) The experts disagree, however, on the meaning of the phrase "can be used". This question is at the crux of the disagreement between the parties on both the "promise" of the '203 Patent and the nature of the invention.

[107] The disclosure continues for several pages with a description of preferred embodiments (pages 9-12), a description of the process for preparing the compounds (pages 12-25) and descriptions of 32 examples that "illustrate the invention" (pages 25-35). Of particular relevance, Example 21 (page 31) is imatinib.

[108] The balance of the specification consists of the 48 claims. Broadly speaking, the claims are divided into four categories, directly matching the initial paragraph of the disclosure:

- Claims 1-39 claim compounds, with Claims 1 to 8 consisting of compounds described in terms of their possible chemical substitutions for R_1 to R_8 in formula I and Claims 9-39 consisting of individual compounds, all of which fall within one or more of Claims 1 to 8;

- Claims 40-43 cover pharmaceutical compositions for particular treatments;

- Claim 44 is a claim to the process for preparation of the compounds of formula I;

- Claims 45-48 are claims to the use of the compounds according to <u>any one of</u> claims 1 to 39 for the preparation of a pharmaceutical composition for use in the treatment of atherosclerosis (Claim 45), use in the chemotherapy of tumours (Claim 46), chemotherapy treatment of tumours (Claim 47) and treatment of atherosclerosis (Claim 48).

[109] Based on the many possible chemical substitutions at R_1 to R_8, the class of compounds covered by Claim 1 is exceedingly large, as acknowledged by the experts, likely extending to billions of compounds.

[110] The claims which follow begin to narrow the selection. Claims 5 and 7 are of particular interest:

> 5. A compound of formula I according to claim 1, wherein
> R_1 is pyridyl or N-oxido-pyridyl each of which is bonded at a carbon atom,
> R_2 and R_3 are each hydrogen,
> R_4 is hydrogen or lower alkyl,
> R_5 is hydrogen, lower alkyl or trifluoromethyl,
> R_6 is hydrogen,
> R_7 is nitro, fluoro-substituted lower alkoxy or a radical of formula II wherein
> R_9 is hydrogen,
> X is oxo
> N is the number 0 and
> R_{10} is pyridyl bonded at a carbon atom, phenyl that is unsubstituted or substituted by halogen, cyano, lower alkoxy, carboxy, lower alkyl or by 4-methyl-piperazinyl-methyl, or C_5-C_7 alkyl, thienyl, 2-naphthyl or cyclohexyl, and
> R_8 is hydrogen.
> or a pharmaceutically acceptable salt of such a compound having at least one salt-forming group.
>
> 7. A compound according to any one of claims 1 to 5 of formula I, wherein at least one of the radicals R_4 and R_8 is lower alkyl, or a pharmaceutically acceptable salt of such a compound having at least one salt-forming group.

[111] Claim 7 encompasses only compounds from Group 2 because, as stated by Dr. Rönnstrand (TX 13, para 109):

> at least one of the chemical groups substituted at positions R_4 and R_8 must be a lower alkyl group and, therefore, Group 1 compounds are excluded because they are required to have only hydrogen atoms at positions R_4 and R_8.

[112] The experts agree that Claims 9-27 and 34-39 cover compounds that are within Group 1. They also agree that the compounds of Claims 28-33 belong to Group 2 and Claim 29 is to the compound imatinib.

[113] The "use" claims – Claims 45 to 48 all refer to the "use of a compound of formula I according to any one of claims 1 to 39" (emphasis added). One example of how the compound claims should be read together with the use claims is that Claim 29 together with Claim 46 means a claim to imatinib when used in the chemotherapy of tumours. The experts acknowledge that the use of imatinib to treat CML is a use that would be considered the "chemotherapy of tumours".

[114] One very important point of agreement among the experts was that a person of ordinary skill in the art would be able to recognize that the '203 Patent includes compounds within two classes – Group 1 and Group 2. There was some lack of clarity about Group 1A compounds; no expert identified any Group 1A compounds in the examples or the specific claims of the patent. However, the '203 Patent clearly delineates which of the examples and specifically-claimed compounds belong to Group 1 and which to Group 2. Further, the skilled person would also know the key attributes of each of these two groups or sub-classes. Specifically, the Group 1 compounds selectively inhibit PKC. Subject to the dispute surrounding the meaning of "and", the Group 2 compounds selectively inhibit PDGF-R and ABL, but not PKC.

[115] The submissions of the parties raise serious issues of construction of the '203 Patent.

[116] The first question has been referred to as the "and/or" issue. Should the '203 Patent – and Claim 46 in particular – be read such that every one of the claimed Group 2 compounds is capable of treating both tumours which are driven by PDGF-R and tumours driven by ABL

kinases? Or, is the more appropriate construction one where each of the Group 2 compounds may treat either a PDGF-R driven tumour or an ABL-driven tumour?

[117] The second issue relates to the meaning of "can be used" as presented in the disclosure.

[118] Finally, in this section, I will address the question of whether the '203 Patent discloses any data or test results for ABL kinase inhibition by the Group 2 compounds.

[119] Another broad area of concern relates to the intent or breadth of the '203 Patent. In language useful for an analysis of the utility of the patent, what is the "promise" of the '203 Patent? In a similar vein, the question relevant to an examination of the sufficiency of the disclosure is this: what is the nature of the invention? These two questions will be dealt with in the applicable sections of these reasons.

D. *The "and/or" Question*

[120] A central construction question is whether Claim 46 should be construed to mean that every Group 2 compound is a selective inhibitor of both PDGF-R and ABL kinases. Or, is the more reasonable construction one where each of the Group 2 compounds is a selective inhibitor of either PDGF-R or ABL? Claim 46 is a claim to:

> 46. A use of a compound of formula I according to any one of claims 1 to 39 or a pharmaceutically acceptable salt of said compound having at least one salt-forming group for the preparation of a pharmaceutical composition for use in the chemotherapy of tumours.

[121] The Plaintiffs submit that the proper construction of Claim 46 is that each of the Group 2 compounds is useful in the treatment of both PDGF-R and ABL-driven tumours. The term "tumours" is not defined in the claims; the reader must turn to the disclosure to assist.

[122] The paragraph that appears to address this issue is at page 7 of the disclosure:

> Some of the compounds of formula I wherein R_4 and R_8 are hydrogen inhibit not only protein kinase C but, at a concentration IC_{50} as low as approximately from 0.01 to 5 μmol/litre, especially approximately from 0.05 to 1 μmol/litre, also certain tyrosine kinases, such as especially PDGF-receptor kinase or abl-kinase, for example v-abl-kinase. Compounds of formula I wherein at least one of the radicals R_4 and R_8 is other than hydrogen and is, for example, lower alkyl, such as methyl, are especially selective for the above-mentioned PDGF-receptor and abl-tyrosine kinases and inhibit protein kinase C virtually not at all.

[123] All of the experts agree that the first sentence of this paragraph refers to a separate group of compounds referred to as the Group 1A compounds. The Group 1A compounds are described with these words:

> [The Group 1A compounds] inhibit not only protein kinase C but . . . also certain tyrosine kinases, such as especially PDGF-receptor kinase or abl-kinase . . . [Emphasis added.]

[124] This same paragraph continues with a sentence referring to the Group 2 compounds:

> [Group 2 compounds] are especially selective for the above-mentioned PDGF-receptor and abl-tyrosine kinases and inhibit kinase C virtually not at all. [Emphasis added.]

[125] The Plaintiffs submit that the inventor chose to use the word "or" to describe the function of the Group 1A compounds. Reading this sentence in association with Claim 46, a reader would

understand that some Group 1A compounds would be useful to treat tumours driven by PDGF-R, while others could treat ABL kinase-driven tumours.

[126] In contrast, the Plaintiffs assert that, by choosing the word "and" in association with the Group 2 compounds, the inventor leads the notional reader to understand that every one of the Group 2 compounds would be useful for treatment of tumours associated with either PDGF-R or ABL kinases. It follows, in the view of the Plaintiffs, that the word "tumours" in Claim 46 means that any compound of Group 2 can treat both PDGF-R and ABL-driven tumours. Thus, they argue that a Group 2 compound that inhibits PDGF-R but not ABL does not meet the promise of the patent that the compounds would be useful for "the chemotherapy of tumours".

[127] Dr. Rönnstrand, with no reasoning or analysis, adopts the "and" construction (TX 13, para 79):

> In my opinion, the person skilled in the art would have understood the above passage from the 203 Patent to say that the compounds of Group 2 inhibit both the PDGF-R and Abl protein kinases, but do not inhibit appreciably PKC (or at all). In other words, the compounds of Group 2 are said to have activity against each of PDGF-R and Abl protein kinases, but exhibit no inhibition of PKC.

[128] The English word "and" is notoriously ambiguous. I do not need an expert in medicinal chemistry to tell me that the word "and" takes its meaning from its context. The problem with the interpretation put forward by the Plaintiffs and Dr. Rönnstrand is that it fails to consider the context of the entire paragraph in which the "and" reference is placed. The first part of the paragraph speaks to the inhibitory qualities of Group 1A compounds. As I read the second part of the paragraph, containing the explicit reference to the Group 2 compounds, it is specifically

outlining the selectivity of these particular compounds. It incorporates by reference and builds on the first part of the paragraph. In other words, the inventor is telling the reader that these Group 2 compounds have the same characteristics of the Group 1A compounds, but they are more selective because they do not inhibit PKC. The words "the above-mentioned PDGF-receptor and abl-tyrosine kinases" must be linked to the first sentence that speaks of PDGF-R and ABL in disjunctive terms. Read as a whole, this paragraph supports a reasonable interpretation that the Group 2 compounds may be inhibitors of either PDGF-R or ABL kinases.

[129] This construction also is consistent with the known science of tumours in 1993. As explained by Dr. Van Etten in his Expert Report (TX 37, para 111):

> I would read the Patent as relating to either PDGF-R *or* ABL-kinase tumours. In 1993 it was known that tumours associated with activated PDGF-R or with activated ABL kinase are distinct. That is, there are no examples either in 1993 or today of tumours that are associated with activation of both kinases.

[130] This statement makes sense. Knowing this information in 1993, a person of ordinary skill in the art would, in my view, conclude that the '203 Patent discloses that the treatment attributes of Group 2 compounds relate to either PDGF-R or ABL-kinase tumours.

[131] The Plaintiffs assert that Dr. Heldin, during his cross examination, agreed that the patent promises therapeutic treatment of PDGF-R-related tumours and ABL-related tumours (14T2740-2743). In describing the properties of Group 2 compounds, one may state that they inhibit PDGF-R and ABL kinases, as Dr. Heldin did during his testimony. However, these comments did not, in my view, address the controversy over the use of the word "and". Dr. Heldin's point, given the context, appears to be that use of a Group 2 compound according to

Claim 46 can relate to the treatment of two types of tumours – those associated with PDGF-R and those associated with ABL kinase. It is a huge and contrived step to interpret a statement such as this as an opinion that a Group 2 compound that inhibits PDGF-R but not ABL does not meet the promise of the patent that the compounds would be useful for "the chemotherapy of tumours", especially since Dr. Heldin clearly took the opposite position in his report (TX 71, para 114). The Plaintiffs have taken Dr. Heldin's general remarks out of context.

[132] In support of their position on this issue, the Plaintiffs refer to my decision in *Schering-Plough Canada Inc v Pharmascience Inc,* 2009 FC 1128, 81 CPR (4th) 9 [*Desloratadine (FC)*] in which case I had the occasion to review the meaning of the word "or" in a patent.

[133] Claim 1 of the patent under consideration in *Desloratadine (FC)*, above at paragraph 76, was a claim to "a pharmaceutical composition". Claim 9 of the patent was to:

> The pharmaceutical composition of claim 1 wherein the composition is present in one of tablet or capsule form.

[134] The applicant in that case, Schering-Plough Canada Inc (Schering-Plough), submitted that Claim 9 defined the subject matter of the invention in the alternative – that the claim described the invention as being in one of tablet or capsule form (para 89). Thus, Schering-Plough argued, even if I were to find that the capsule form of the compound was anticipated by the prior art, the tablet form of the drug could be treated as a separate claim and upheld. I did not accept this argument and found all of Claim 9 to be invalid for anticipation.

[135] The interpretation that I applied in *Desloratadine (FC)* to Claim 9 is, in the view of the Plaintiffs, consistent with the construction that they promote for the word "tumours" in Claim 46 and the use of the word "and" in the disclosure.

[136] A key factor to the meaning that I ascribed to the phrase "tablet or capsule" in that case is found at paragraph 78 of *Desloratadine (FC)*, where I stated the following:

> Claim 9 captures either tablet or capsule forms of the "pharmaceutical composition of claim 1". No expert appears to dispute that conclusion. [Emphasis added.]

[137] The flaw in the Plaintiffs' reliance on *Desloratadine (FC)* is that no expert, in that case, provided any contrary meaning of the phrase "tablet or capsule". In contrast, before me in this case, I have opposing views from Dr. Van Etten and Dr. Rönnstrand. Unlike *Desloratadine (FC)*, in this case, I must consider the alternative construction. The conclusion that I reached in *Desloratadine (FC)*, involving a different patent and different issues and with no dispute from the experts on the meaning of the term, cannot be said to provide me with a meaningful precedent.

[138] In summary on this issue, I conclude that it is not a reasonable construction of the '203 Patent to conclude that the word "tumours" in Claim 46 means that any compound of Group 2 can treat both PDGF-R and ABL-driven tumours. Rather, the meaning to be ascribed to Claim 46 of the '203 Patent is that a Group 2 compound may be useful to treat either PDGF-R or ABL tumours.

E. *Meaning of "can be used"*

[139] The next disagreement between the parties revolves around the words "can be used" as seen in several places in the disclosure.

[140] The '203 Patent makes extensive reference to the intended use of the compounds. The first of these references is at page 5, fourth full paragraph, where the author states:

> The compounds of formula I have valuable pharmacological properties and can be used, for example, as anti-tumoral drugs and as drugs against atherosclerosis.

[141] A second reference is contained on page 6, second full paragraph, where the uses of the Group 1 compounds are described as follows:

> Owing to their inhibiting activity towards protein kinase C, the compounds of formula I ... can be used as tumour-inhibiting . . .ingredients ...

[142] A similar statement is made with respect to the Group 2 compounds (third full paragraph, p. 8).

[143] Does the use of the word "can" when referring to the therapeutic use of the compounds mean that the compounds are guaranteed to treat the described medical conditions? This appears to be the position of the Plaintiffs. As presented in oral argument (15T2970):

> [R]eally the debate between the parties is whether "can be used" means "might be used" or "potential for use." My friend's position is that is what someone takes from the words "can be used."
>
> We submit that the words "can be used" connote a radically different meaning to "might be used" or have "potential for use.

[144] The experts were in disagreement on this question. In his report and throughout his oral testimony, Dr. Rönnstrand promoted a meaning of the word "can" to mean a certainty. In contrast, Drs. Van Etten and Heldin took a position that the skilled person would understand the words of the patent to mean something less than certainty. For example, in his report (TX 71, para 129), Dr. Heldin stated that "compounds such as imatinib have the potential to be useful in treatment of tumours or atherosclerosis" (emphasis added). In final argument, the Plaintiffs wrote that:

> The words "might" and "potential" were repeatedly injected into Novartis' experts' construction of the patent, notwithstanding that those words are never used in the patent in the manner suggested by Novartis' experts.

[145] The first argument of the Plaintiffs is that the words used by the author of the patent are "can be used" and not "the potential to be used". That is correct. However, it is not determinative.

[146] In the *Canadian Oxford Dictionary*, 2d ed, sub verbo "can", the word "can" has at least two meanings. It can mean "be able to"; this would support the position of the Plaintiffs. However, it can also mean "be potentially capable of"; this accords with the view of Novartis. To establish a purposive meaning for the phrase "can be used", we need to look to the context and subject matter of the '203 Patent.

[147] The Plaintiffs rely on the decision of my colleague, Justice Boivin, in *Apotex Inc v Sanofi-Aventis*, 2011 FC 1486, 101 CPR (4th) 1 [*Clopidogrel*], where Justice Boivin was faced with a similar question of interpretation of the words "can be usefully administered in the

treatment and prevention of platelet disorders" in the patent at issue. While acknowledging that the words did not make reference to a guaranteed treatment in humans, he concluded that:

> [T]he 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 potential: it can be used in the treatment of certain human thrombotic diseases." [emphasis in original]

[148] Absent the entire record before Justice Boivin in *Clopidogrel*, I cannot have a full understanding of how he came to this finding or what he meant by "more than potential". However, I observe that he rejected any argument of a "guarantee" and, from the emphasis he added to his conclusion, that he was focussed on the words "used" and "human". In sum, I do not take this citation as an authority that is either contrary to my conclusion on this question or binding on me.

[149] In the context of the '203 Patent and the world of cancer research, the word "can" does not convey a meaning of certainty; rather it should be equated to the term "potential". I will agree that the use of "can" in this context implies more than pure speculation or lucky guess. I also accept that the word "can be used" means more than "might be used"; a potential for use is certainly a higher threshold than "might". In other words, there must be substance to the link between the claimed use and cancer treatment.

[150] I also see that the '203 Patent includes words that imply a certainty with respect to the inhibitory properties of the claimed compounds. The '203 Patent states that the compounds "have valuable pharmacological properties". There is no potential or lack of certainty with this phrase,

suggesting that, for the inhibition properties, the author is providing the reader with a very strongly held position – almost guarantee – that the compounds will be selective inhibitors of the named kinases. However, by using the words "can be used" elsewhere, arguably, the author meant something less than certainty.

[151] In conclusion on this construction issue, I prefer the opinions of Drs. Heldin and Van Etten. I conclude that the notional skilled person would read the phrase "the compounds . . . can be used" in the '203 Patent to mean that the compounds have the potential, demonstrated or predicted, to be used as "tumour-inhibiting active ingredients".

F. *Disclosure of ABL data*

[152] The Plaintiffs assert that the '203 Patent "provides no factual basis whatsoever upon which any prediction that Group 2 compounds could treat Abl-related tumours could be based". Specifically, the Plaintiffs look to the second full paragraph at page 8 which contains the only specific mention of ABL testing:

> The above-mentioned inhibition of v-abl-tyrosine kinase is determined in accordance with the methods of N. Lydon et al . . .

[153] The Plaintiffs interpret this paragraph as follows:

> A person of skill in the art would not have read this portion of the patent and understood it to indicate that a v-Abl inhibition assay had been run, but rather that an assay could be run. This is particularly so since no IC_{50} values or even ranges from this assay are provided, notwithstanding that exemplary ranges of IC_{50} values for each and every other test referenced in the patent are given.

[154] It is true that this particular paragraph contains no IC_{50} values. However, the beginning words – "the above-mentioned inhibition of v-abl-tyrosine kinase" – refer the reader to the inhibition values set out earlier in the patent. In his report (TX 13, para 85), Dr. Rönnstrand opined that the '203 Patent did not provide any data with respect to ABL testing. However, during cross-examination, he acknowledged that the IC_{50} values set out at page 7 of the '203 Patent were both "PDGF and ABL ranges" (4T748-750). The explanation for the statement in his report was that:

> It's a range given for two kinases, so we can't say this is a range for PDGF and this is a range for Abl. That's what I meant.

[155] Reading the paragraph on page 8 in context with the IC_{50} values stated earlier, the '203 Patent discloses a range of IC_{50} values for inhibition of v-ABL of "0.01 to 5 µmol/litre, especially approximately from 0.05 to 1 µmol/litre" (page 7, third full paragraph).

[156] I also do not agree with the opinion of the Plaintiffs that the paragraph only discloses that "an assay *could* be run". This is simply a reading of the patent characteristic of a mind unwilling to understand.

[157] I am satisfied that a skilled person reading this paragraph of the patent would understand that the assays, using those methods described, had been run and that a range of IC_{50} values in respect of ABL inhibition are disclosed earlier in the patent.

G. *Conclusion on Construction*

[158] Subject to the later discussion of the promise of the patent and nature of the invention, I am satisfied that a person of ordinary skill in the art would construe the '203 Patent, insofar as the parties disagree, as follows:

1. the meaning to be ascribed to Claim 46 of the '203 Patent is that a Group 2 compound may be useful to treat either PDGF-R or ABL tumours.

2. the phrase "the compounds . . . can be used" means that the compounds have the potential, demonstrated or predicted through reasonable inferences, to be used as stated in the '203 Patent.

3. ABL inhibition testing had been carried out, using those methods described in the second paragraph of page 8, with a range of IC_{50} values as disclosed earlier in the patent.

VII. Utility: Principles and Promise

A. *Principles*

[159] Section 2 of the *Patent Act* specifies than an "invention" may be "any new and useful…composition of matter, or any new and useful improvement". Thus, the "invention" of the '203 Patent must be both "new" and "useful".

[160] The Plaintiffs do not dispute that the compounds of the '203 Patent were new or novel. Their principle argument is that, as of the Canadian filing date of April 1, 1993, the inventor could not show that the "invention" of the patent was useful. In other words, the Plaintiffs assert that the '203 Patent does not have "utility" as that term has been explained by and applied in the jurisprudence.

[161] Utility is determined at the Canadian filing date based on the state of the art and information available at that time (*Aventis Pharma Inc v Apotex Inc*, 2006 FCA 64 at para 30, 265 DLR (4th) 308; *Eli Lilly Canada Inc v Novopharm Ltd*, 2010 FCA 197 at para 74, [2012] 1 FCR 349 [*Olanzapine*]; *Apotex Inc v Pfizer Canada Inc*, 2011 FCA 236 at para 17, 95 CPR (4th) 193 [*Latanoprost*]). Evidence and knowledge available after the filing date cannot establish utility (*Apotex Inc v Wellcome Foundation Ltd*, 2002 SCC 77 at para 46, [2002] 4 SCR 153 [*AZT*]).

[162] As taught by *AZT* and other cases, even if utility is not demonstrated at the filing date, the utility requirement may be met through sound prediction (*AZT*, above at para 46). While the patent in *AZT* related to a new use (treatment of HIV/AIDS) for an old chemical compound (AZT), the Court of Appeal has held that the doctrine of sound prediction applies to a claim for a new compound (*Pfizer Canada Inc v Apotex Inc*, 2007 FCA 195 at para 3, 60 CPR (4th) 177). A sound prediction requires that the patentee provide "a solid teaching", and it cannot protect "a lucky guess" or "mere speculation" (*AZT*, above at paras 69, 83). A patentee does not have to explain exactly why the invention works, but must provide the underlying knowledge supporting that it does work (*AZT*, above at para 70).

[163] Sound prediction is a question of fact (*AZT*, above at para 71). A sound prediction must meet three requirements (*AZT*, above at para 70):

1) There must be a factual basis for the prediction;

2) There must be an articulable and sound line of reasoning connecting the desired result and the factual basis; and

3) There must be proper disclosure of the factual basis and line of reasoning in the patent.

The Court of Appeal has recently summarized these three indicia as a general requirement for "a *prima facie* reasonable inference of utility" (*Olanzapine*, above at para 85).

[164] Sound prediction is not a free-standing statutory requirement. Rather, it is a way of showing that an invention is useful when the invention has not been directly demonstrated to work. Its introduction into Canadian law was not, as I understand it, to give a crushing hammer to those who challenge patents.

[165] As noted by Justice Dickson in *Consolboard*, above at 525-526, an invention lacks utility if it is demonstrated that the invention "will not operate at all or, more broadly, that it will not do what the specification promises that it will do" (emphasis added). This has given rise to the concept of the "promise of the patent", which has been a major area of disagreement in this trial.

[166] The promise of the patent should be determined at the outset of the utility analysis in a purposive manner (*Olanzapine*, above at para 93; *Latanoprost*, above at para 17). If the inventors do state a specific promise in the patent, the court must evaluate utility against this promise (*Pfizer Canada Inc v Mylan Pharmaceuticals ULC*, 2011 FC 547 at para 212, 93 CPR (4th) 193 [*Donepezil (FC)*], aff'd 2012 FCA 103, 100 CPR (4th) 203 [*Donepezil (FCA)*]; *Olanzapine*, above at para 93). Just a mere scintilla of utility is insufficient in the face of a specific promise that requires more (*Novopharm Ltd v Eli Lilly and Co*, 2011 FCA 220 at paras 31-34, 94 CPR (4th) 95).

[167] The promise of the patent is a question of law assessed by the court from the perspective of a skilled person, with the assistance of expert evidence (*Olanzapine*, above at paras 80, 93).

[168] One of the more recent statements of the applicable principles of both utility and promise is contained in *Donepezil (FCA)*, above at paragraph 57:

> Though some references are made in the '808 Patent to potential toxicity and efficacy benefits of donepezil, and to its potential advantages over prior art compounds, the application judge, on the basis of the expert evidence before him, rightly concluded that these references are not to be construed as promises. He noted that the use of the specification of a patent in order to construe its promise "is not to serve as an invitation to a zealous lawyer to read a patent specification in such a way as to persuade a Court, one way or the other, as to what the promise is": Reasons at para. 213. As recently aptly noted by Zinn J. of the Federal Court, "the jurisprudence does not permit an unescorted and unchaperoned romp through the disclosure": *Janssen-Ortho Inc. v. Canada (Health)*, 2010 FC 42, 82 C.P.R. (4th) 336 at paras. 119-120. The disclosure in the specification is to be understood from the viewpoint of a skilled person in the art or science to which the invention pertains, without resort to technicalities but rather for the purpose of seeking a construction of the claims which is reasonable and fair for both the patentee and the public: *Consolboard Inc. v. MacMillan Bloedel (Sask.) Ltd.*, [1981] 1 S.C.R. 504 at pp. 520-21.

B. *The Promise of the '203 Patent*

(1) Parties' Positions on the Promise of the Patent

[169] Utility must be assessed against the promise of the '203 Patent. The parties disagree on what the promise is.

[170] In final argument, the Plaintiffs submitted that there are three components to the promise, as follows (15T2967):

> First, what is promised in this patent – and this applies to all of the claims for the reasons I told you earlier – is an *in vivo* therapeutic effect. Let's start there.

> The second aspect of the promise is that the *in vivo* therapeutic effect is to treat something, and I will be focusing on treating tumors.
>
> And, finally, we submit that the tumors to be treated will be those associated with PDGF-R and those associated with Abl. And what that means, in our submission, is that if either of those two types of tumors had not been demonstrated or soundly predicted could be treated by these compounds, then the compound would fail for lack of utility.

[171] I have already addressed the third component of the alleged promise in the section of these reasons dealing with the construction of the patent. This is the "and/or" argument. I do not accept that the skilled person would read Claim 46 to mean that the patent promises that each compound would treat diseases associated with both PDGF-R and ABL. As long as the compound works as promised against either PDGF-R or ABL associated diseases, it will meet the promise of the patent.

[172] The next question is whether the "promise" amounts to a near certainty, as argued by the Plaintiffs. As discussed above in the section of these reasons dealing with the construction of the claims, the words "can be used" should be interpreted to mean that the compounds have the potential to be used in the ways described. In this context, "potential" must mean more than speculation or lucky guess; there must be either demonstrated utility or sound prediction that the compounds would work *in vivo*. What remains is the Plaintiffs' assertion that every claim of the '203 Patent promises an *in vivo* therapeutic effect.

[173] Novartis's position on the promised utility of the patent has two aspects depending on whether we are focussing on the compound claims or the use claims:

1. The promised utility of the compound claims is that these compounds are selective inhibitors of particular kinases;

2. The promised utility of Claim 45, when read together with Claim 7 or Claim 29, is the use of these compounds, as selective inhibitors of PDGF-R, to treat atherosclerosis; and

3. Claim 46, when read together with Claim 29, is the use of imatinib for the chemotherapy of tumours.

(2) Differentiated Utility or Promise

[174] The Plaintiffs submit that every claim must have the same utility. In my view, this just does not accord with the reality of the '203 Patent. From the first paragraph in the '203 Patent, the skilled reader is informed that there are four aspects to the patent and four groups of claims that match those aspects. The author states that the invention relates to:

1. the compounds themselves (N-phenyl-2-pyrimidine-amine derivatives);

2. processes for the preparation of the compounds;

3. medicaments comprising those compounds; and

4. the use of those compounds for the therapeutic treatment of warm-blooded animals.

[175] I cannot think of a clearer delineation of the parts of an invention. In this case, after one reads the entire specification, it becomes very clear that the compound claims are the most important aspect of the patent, with the use claims, the process claim and the medicinal composition claims arising from the properties of the compounds. I observe that there was very little discussion or evidence during the trial addressing the pharmaceutical composition claims – Claims 40 to 42. Moreover, neither Novartis nor the Plaintiffs addressed these particular claims during final argument. I have not considered these claims further.

[176] The '203 Patent further subdivides the claims depending on whether the compounds belong to Group 1 or Group 2. The utility of the compound claims (Claims 1 to 39) is that they selectively inhibit: (a) PKC if in Group 1; and (b) PDGF-R or ABL, but not PKC, if in Group 2. This means that a compound that does not selectively inhibit the relevant enzymes (or cannot be soundly predicted to do so) does not meet the promise of the patent.

[177] The use claims (Claims 45 to 48) are directed at the use of these selective inhibitors for specified maladies and their utility should be assessed on that basis. Thus, if the compound does not have the potential to treat the identified diseases or conditions – tumours for Claims 46 and

47 and atherosclerosis for Claims 45 and 48 – the use claims for that compound do not meet the promise and will not survive.

[178] The structure of the claims in the '203 Patent closely resembles that of the patent before Justice O'Reilly in *Pfizer Canada Inc v Apotex Inc*, 2007 FC 26, 59 CPR (4th) 183 [*Sildenafil I (FC)*] aff'd 2007 FCA 195, 60 CPR (4th) 177). In the patent before Justice O'Reilly, Claim 6 was a claim to a specific compound (sildenafil) and Claim 17 was a claim to the use of the compounds covered by the patent (including sildenafil) for use in the treatment of four particular medical conditions. When it came to consider the utility of the patent, Justice O'Reilly expressed the following views, at paragraphs 41-44:

> As I read the patent, having considered the expert evidence tendered by both parties, there are really two levels of utility referred to in the patent. The first level relates to the properties of the compounds themselves as "potent and selective" cGMP PDE inhibitors. Compounds that manifest those qualities might be useful, for example, for their ability to cause smooth muscles to relax, for their anti-aggregatory or anti-hypertensive effects, or for use in the laboratory. At the second level, because of those inherent properties, the compounds might be useful in the treatment of a wide variety of conditions.
>
> Much of Apotex's argument relates to the lack of demonstrated utility or sound prediction in relation to the compounds' use in treating the conditions named in the patent. However, I agree with Pfizer that, at least for its Claim 6 (which is a claim for the compound sildenafil alone) it is enough if Pfizer can prove that sildenafil had a useful property (i.e. potent and selective cGMP PDE inhibition) that may make it suitable for use in the treatment of certain diseases or conditions, or for use in the laboratory. In doing so, Pfizer would show that its product met the definition of an "invention" set out in the Act. I am satisfied from the evidence that, at the priority date of the patent, it was expected that PDE inhibitors could be useful in the treatment of certain conditions. Scientists were looking for compounds that were more potent and selective cGMP inhibitors than were currently available. Accordingly, for Claim 6, Pfizer merely has to show that sildenafil

> had been demonstrated, or soundly predicted, to be useful simply by virtue of its capacity to act as a potent and selective cGMP PDE inhibitor.
>
> However, where the patent is more specific and claims that a compound is actually useful for the treatment of particular diseases and conditions, the patentee must show the compound's utility in those areas. Accordingly, for Pfizer's Claim 17 (which is a claim for the compounds' use in particular treatments), it must demonstrate actual utility, or establish that utility was soundly predictable, in those areas. But Pfizer can only be successful in defending Claim 17 if it succeeds in defending Claim 6. Proof of sildenafil's utility in the treatment of the conditions named in Claim 17 (i.e. angina, hypertension, heart failure or atherosclerosis), or a sound prediction that it would be useful for that purpose, is obviously dependent on proof that sildenafil was known (or soundly predicted) to be a potent and selective cGMP PDE inhibitor in 1990.

[179] As pointed out by the Plaintiffs, Justice O'Reilly did not follow this approach in the later decision of *Eli Lilly Canada Inc v Novopharm Ltd*, 2011 FC 1288, 100 CPR (4th) 269. However, a careful reading of that later decision highlights that the disclosure and claims of the patent in this later case were much different. The entire basis of the selection patent at issue was that olanzapine treats schizophrenia in the clinic better than other antipsychotic drugs; there was no basis on which to apply a different promise to any of the claims. In the '203 Patent and in the patent considered in *Sildenafil I (FC)*, we have no such overarching promise.

[180] If I follow the reasoning of my colleague in *Sildenafil I (FC)*, the claimed utility for those claims in issue (Claims 1-39, 44-48) would be differentiated on the basis of the aspect of the claims. The promised utility would be as follows:

1. For Claims 1 to 39, the promise or utility is that the compounds will selectively inhibit PKC, PDGF-R or ABL. That is all.

2. For Claims 45 to 48, the patent provides a more explicit utility: that a compound included in Claims 1 to 39 can be used to treat atherosclerosis (Claims 45 and 48) and for the "chemotherapy of tumours" (Claims 46 and 47). In my view and in the opinion of the experts, this would incorporate the notion of *in vivo* efficacy – either demonstrated or soundly predicted (see, for example, Dr. Van Etten at 8T1602).

3. For Claim 44, the utility is to provide a process to make the claimed compounds.

[181] The Plaintiffs point to an exchange between counsel and Dr. Van Etten during his cross examination where he appears to agree that even the individual compound claims must be claims to compounds that would have *in vivo* efficacy. That conversation is as follows (8T1601-1602):

> Q. The compound claims, where there's an individual compound claim, wouldn't you agree with me that it's a reasonable reading of this patent that those claims are to compounds that would have in vivo therapeutic efficacy?
>
> A. It may have.
>
> Q. Let's look at the patent.

A. You're talking about any individual compounds now?

Q. Yes?

A. As a group the claim is some of them.

Q. Claim 29 is one compound?

A. That's correct.

Q. Wouldn't it be a reasonable interpretation that that compound is promised to have therapeutic efficacy in vivo in people?

A. No.

Q. Why do you say that?

A. You said in people.

Q. Okay. In animals?

A. Yes. They said treatment of tumours which, by definition, has to occur *in vivo*.

[182] With all due respect to Dr. Van Etten, I do not believe that he had a clear understanding of the term "promise of the patent". The term "treatment of tumours" is not contained in the compound claims. It appears that Dr. Van Etten was considering the use claims in association with the compound claims; for example, Claim 46 together with Claim 29.

[183] I accept that the use claims of the '203 Patent promise some *in vivo* efficacy in warm-blooded animals. As discussed above, however, this is not a guarantee or certainty, as is the case with the inhibitory attributes of the compounds; rather, these claims promise the potential of *in vivo* treatment of the named maladies or conditions.

[184] By way of an example which became the focus of much of this trial, Claim 46 when read together with Claim 29, promises that imatinib: (a) will inhibit PDGF-R or ABL kinases; and (b) will have the potential to treat tumours in warm-blooded animals.

(3) Dr. Rönnstrand's Opinion on Promise

[185] Dr. Rönnstrand expressed very strongly held views on the promise of the '203 Patent, which views were contrary to the opinions of Drs. Heldin and Van Etten. There are three aspects of his opinion that I wish to address:

1. Dr. Rönnstrand's opinion that the promised use is to treat disease in warm-blooded animals;

2. His view that the '203 Patent unconditionally promises such utility; and

3. His conclusion that the Group 2 compounds promise inhibition of both ABL and PDGF-R kinases.

[186] Dr. Rönnstrand stated that the '203 Patent promises that "the compounds can be used in the treatment of a disease or condition in a warm-blooded animal" (TX 13, para 41) and that "the use of the term 'valuable pharmacological properties' indicates that the compounds of formula I would exhibit beneficial biological activity in a living organism, such as a warm-blooded

animal" (TX 13, para 45). Dr. Rönnstrand refines this opinion later in his report, depending on whether the compounds belong to Group 1 or Group 2:

> In my opinion, the person skilled in the art would have understood the promised utility of a compound of Group 1 to be the treatment of diseases and conditions in warm-blooded animals, where one or more PKC isozyme(s) has a causative role because the compound is selective for the one or more PKC isozyme(s). (TX 13, para 100)
>
> In my opinion, the person skilled in the art would have understood the promised utility of a compound of Group 2 to be the treatment of diseases and conditions in warm-blooded animals, where either PDGF-R or Abl protein kinases have a causative role because the compound is selective for each of PDGF-R and Abl, while being a weak or non-inhibitor of PKC isozymes. (TX 13, para 102)

[187] I begin by agreeing with Dr. Rönnstrand that "[T]he person skilled in the art would have understood the promised utility of the 203 Patent to be dependent on what 'Group' the compound belongs to" (TX 13, para 99). However, the problems that I have with Dr. Rönnstrand's opinion extend beyond his delineation of Group 1 and 2 compounds.

[188] In his reports, Dr. Rönnstrand is treating the entire patent as a use patent. The '203 Patent is primarily a compound patent; the potential uses arise from the fact that selective inhibition of the identified kinases is a valuable pharmacological property that can lead to therapeutic use. As admitted by Dr. Rönnstrand, selective inhibition is, in and of itself, a valuable pharmacological property. By leaping to the secondary component of the patent – the potential use arising from the selective inhibitory attributes of the compounds – Dr. Rönnstrand ignores (or seriously discounts) the obvious utility of the compounds as selective kinase inhibitors.

[189] The second key component of Dr. Rönnstrand's expert opinion is exemplified by his statement that, "the compounds of Group 1 have utility in the treatment of one or more of the listed diseases/conditions in warm-blooded animals. . . . the underlying presumption being that the listed diseases/conditions are therapeutically treated by the selective inhibition of one or more PKC isozyme(s) *in vivo*" (TX 13, para 59).

[190] Dr. Rönnstrand understands the patent to deliver – unequivocally – therapeutic treatment. As I have discussed in the section of these reasons on Construction, I do not accept that the '203 Patent promises such certainty; nor does the law require such unconditional certainty. All that is required is a reasonable inference and that the words of the patent meet the requirements of sound prediction.

[191] My final issue with Dr. Rönnstrand's opinion is his view that "the compounds of Group 2 inhibit both the PDGF-R and Abl protein kinases but do not inhibit appreciably PKC (or at all)" (TX 13, para 79). This is the "and/or" question, which I have dealt with above. I disagree with Dr. Rönnstrand's premise that each of the Group 2 compounds will inhibit both PDGF-R and ABL.

[192] In sum, I have serious problems with Dr. Rönnstrand's approach to and conclusions with respect to the promise of the patent. I wish to emphasize, however, that Dr. Rönnstrand was exceedingly patient and careful in his explanations of the science underlying the '203 Patent. Dr. Rönnstrand is a fine scientist and was a credible expert witness.

(4) Claim 44

[193] Turning to Claim 44, a claim to the process for making the compounds of formula I, all of the experts agreed that the various steps in making the compounds would have been known to the person of ordinary skill in the art. As stated by Dr. Rönnstrand, if the compounds of formula I do not have utility, then Claim 44 does not have utility either (Rönnstrand Report, TX 13, para 116; 3T446). However, as Dr. Wuest opined, while the types of reactions used in the process claim were known, none of them had been applied to the starting materials to create the end products of the '203 Patent. If the compounds are novel and useful, the process to make them is also novel (Wuest Report, TX 53, para 44; 9T1842-1844). I agree.

(5) Conclusion on Promised Utility

[194] For these reasons, I conclude that the promised utility would be as follows:

1. For Claims 1 to 39, the promise is that the compounds will selectively inhibit PKC, PDGF-R or ABL.

2. For Claims 45 to 48, the patent provides the reader with a specified promise of *in vivo* utility: that a compound included in Claims 1 to 39 can be used to treat atherosclerosis (Claims 45 and 48) and for the "chemotherapy of tumours" (Claims 46 and 47). In my view and in the opinion of the experts, this would

incorporate the notion of *in vivo* efficacy – either demonstrated or soundly predicted (see, for example, Dr. Van Etten at 18T1602).

3. For Claim 44, the utility is to provide a process to make the claimed compounds.

[195] Accordingly, if Ciba-Geigy had either demonstrated or could soundly predict that, as of April 1, 1993, the compounds of formula I were selective inhibitors of PKC, PDGF-R or ABL kinases, they would have established the utility of those compounds.

[196] During opening submissions, the Plaintiffs conceded as follows (1T72):

> Teva and Apotex concede that if we're unsuccessful in establishing that the 203 promises *in vivo* therapeutic utility with respect to PDGF and v-ABL, Novartis will win because the evidence is clear that *in vitro* activity of claim 29 was established or at least predicted.

[197] This concession goes at least partially to the questions that I am facing in these reasons. The Plaintiffs accept that *in vitro* activity of imatinib (Claim 29) was demonstrated or soundly predicted. Since I have found that the utility of the Group 2 compound claims is that they will be selective inhibitors of either PDGF-R or v-ABL, it follows that the utility of at least Claim 29 has been acknowledged by the Plaintiffs. In spite of this apparent concession, I will consider whether the utility of all of the Group 2 compounds has been demonstrated as of April 1, 1993.

[198] It should be noted that the statement of the Plaintiffs does not extend to the promised utility for Claim 46 when read together with Claim 29. I have found that the use claims of the

patent promise more than *in vitro* selective inhibition. Thus, I must still consider the utility of those claims as measured against the promise that I have found for those compounds.

[199] Establishing the utility of Claims 45 to 48 requires something more than showing that the compounds would selectively inhibit particular enzymes. To meet the promise proffered by those claims, the inventor must satisfy me that the compounds had the potential for the treatment of atherosclerosis (Claims 45 and 48) or chemotherapy of tumours (Claims 46 and 47).

VIII. Utility of the Compound Claims

A. *Demonstrated Utility of the Compound Claims*

[200] From my discussion of the general principles of utility and the promise of the '203 Patent, I turn to a consideration of the question of utility of the compounds of the '203 Patent. In this task, I begin by examining whether utility of the compound claims of the '203 Patent (Claims 1 to 39) had been demonstrated as of April 1, 1993.

(1) General Medicinal Chemistry

[201] Some general medicinal chemistry concepts are directly applicable to my task.

[202] Dr. Heathcock explained that the chemical structures of formula I compounds would allow a skilled person to determine a molecule's size, shape, polarity and

hydrophobicity/hydrophilicity (Heathcock Report, TX 22, para 52). The skilled person would be aware that certain molecules with particular properties would be sufficiently soluble to be effective kinase inhibitors *in vivo* (Heathcock Report, TX 22, para 54; 5T986-989).

[203] Dr. Wuest and Dr. Heathcock acknowledged that a skilled person could distinguish between the Group 1 and Group 2 compounds of the '203 Patent (Heathcock Report, TX 22, para 55; 5T956; Wuest Report, TX 53, Appendix C; 9T1832). Both experts categorized each of the compounds noted in the examples as Group 1 or Group 2 based on their chemical structures.

[204] This is an important consideration and means that it may be possible to draw a reasonable inference that any of the compounds of a general claim – such as Claim 5 or 7 – would have similar inhibitory characteristics to those compounds that have been tested and that are representative of the general claim. The strength of this hypothesis for the particular claims of the '203 Patent is discussed later.

(2) Valuable Pharmacological Properties

[205] I have concluded that the promise of the '203 Patent, as it relates to the compound claims, is that the formula I compounds will exhibit selective inhibition against certain kinases. Two questions arise. First, is selective inhibition a "valuable pharmacological property"; in other words, is a compound with this property useful? Second, as of April 1, 1993, had the compounds of formula I been demonstrated to have the important selective inhibition property?

[206] The answer to the first question is an unqualified "yes". The experts – even Dr. Rönnstrand – agreed that selective kinase inhibition is a "valuable pharmacological property" (4T670). That was a known fact as of April 1, 1993.

(3) Value of *in vitro* Testing

[207] To answer the second question, I begin by reviewing what is necessary to demonstrate that a particular compound selectively inhibits a protein kinase, such as ABL or PDGF-R. It is a commonly held opinion of the experts that selective inhibition can be demonstrated through *in vitro* tests alone. The following exchange between Dr. Rönnstrand and counsel for Novartis is demonstrative of this view (4T661):

> Q. . . . How do you determine that a kinase is a selective inhibitor?
>
> A. By testing it against other kinases and against the kinase that it's supposed to be directed against.
>
> Q. And the type of testing you would do would be an in vitro experiment. Correct?
>
> A. To test the selectivity, yes.
>
> Q. You cannot determine that with an in vivo experiment?
>
> A. No, because it could be influenced by many things.

(4) Ciba-Geigy Testing

[208] Having established that selective inhibition is demonstrated through *in vitro* testing, I turn to the question of whether Ciba-Geigy, as of April 1, 1993, had established that the '203 Patent

compounds, or any of them, had selectively inhibited the kinases referred to in the patent. I will focus on the Group 2 compound claims, including Claim 29 to imatinib, because those are the compounds of the most interest. In particular, the patent discloses (at pages 7-8) that the Group 2 compounds inhibited PDGF-R and v-ABL in a number of *in vitro* tests. For PDGF-R inhibition, the patent clearly sets out that the level of inhibition was in the 1µM range. The skilled reader would have recognized these as impressive levels of inhibition. As discussed earlier in these reasons, it is not unreasonable to read the second paragraph on page 8 as including a reference to the earlier stated inhibition levels for ABL kinase.

[209] These statements are supported by the *in vitro* tests conducted in the Ciba-Geigy laboratories, described below.

[210] Considerable time during this trial was spent on the types of *in vitro* and *in vivo* testing carried out by Ciba-Geigy, the sufficiency of that testing and the reporting of the testing results in the '203 Patent. Briefly, the Plaintiffs submit that Ciba-Geigy did not carry out enough testing to demonstrate – or soundly predict – that the compounds of the '203 Patent meet the promise of *in vivo* therapeutic effects against tumours associated with PDGF-R and ABL kinases. Moreover, because of certain allegedly failed tests, the compounds of Group 2 were demonstrated not to have utility by April 1, 1993.

[211] During the trial, I listened to many criticisms by the Plaintiffs of the testing that was or was not undertaken by Ciba-Geigy before the Canadian filing date. I have some general concerns with respect to the approach taken by the Plaintiffs.

[212] The usual sequencing of *in vitro* testing for inhibition can be summarized in the following way:

Question to be addressed	**Tests**
Can the compound bind to and inhibit the target kinase in the absence of (or outside) the cell membrane?	Cell-free test
Can the compound enter intact cells and inhibit the relevant kinase?	(a) Western Blot test (b) ELISA test
Can the compound inhibit downstream kinase activity induced by a particular enzyme?	(a) MAP kinase test (b) Northern Blot test (or *c-FOS* test)

[213] As explained by the experts, each and every one of these tests can demonstrate the ability (or inability) of the compound to inhibit a target kinase. Not all of these tests were carried out on each of the Group 2 compounds. However, in my view, demonstration of utility does not require that each and every test be carried out on every Group 2 compound.

[214] It is common sense that a compound that responds positively (that is, inhibits a target kinase) in a Western Blot, Northern Blot or ELISA test would also inhibit that kinase in the cell-free test. Stated differently, a compound that can enter a cell and inhibit the kinase can be assumed to be capable of "passing" the cell-free test.

[215] The point that I wish to make is that a review of the *in vitro* Ciba-Geigy testing must be done cumulatively. It is inappropriate to isolate one inconclusive test and hold this up as a demonstration of lack of utility without examining that one test in the context of all the test results for that particular compound.

[216] The situation may be different where a particular *in vitro* test conclusively demonstrates the failure of a compound to inhibit the target kinase. In those circumstances, a serious question of the utility of that compound would be raised. I would also be concerned if the only test carried out on a particular compound was inconclusive. In that case, it would be difficult to conclude that utility had been demonstrated.

[217] A second aspect of the testing program that should be recognized is the chemistry of the compounds. In particular, I have evidence from the experts in medicinal chemistry (Drs. Wuest and Heathcock) about the similarity of the Group 2 compounds. This similarity would enable our skilled person to draw inferences about a Group 2 compound from the testing of another compound. While this may speak more to the notion of sound prediction, it is also a reminder that the testing program of Ciba-Geigy must be reviewed holistically.

[218] In their quest to find fault with specific or omitted tests, the Plaintiffs (and, to some degree, Dr. Rönnstrand in his reports fail to have regard to the whole.

[219] On a general note, Ciba-Geigy measured the results of its tests on 29 compounds in the '203 Patent as IC_{50} values. The potency of an enzyme inhibitor and its selectivity is measured by determining its IC_{50} value. The IC_{50} value represents the concentration of the inhibitor needed to block 50% of the activity of a target enzyme. A potent enzyme inhibitor will have a low IC_{50} value against its target enzyme, demonstrating that a low concentration of the compound is required to inhibit enzyme activity. A selective inhibitor will have a low IC_{50} value against the target enzyme and higher IC_{50} values against other enzymes.

[220] For the assistance of the reader, I provide a table of concordance showing the six individually claimed Group 2 compounds and their respective Ciba-Geigy compound numbers.

Ciba-Geigy Compound #	Claim #
CGP 53716	28
CGP 57148 (imatinib)	29
CGP 57011	30
CGP 57014	31
CGP 57012	32
CGP 57010	33

[221] In addition to falling within the specifically identified claims of the '203 Patent, each of the tested Group 2 compounds is included within Claims 1 to 3, Claim 5 and Claim 7.

[222] In this section of the reasons, I summarize the evidence on the Ciba-Geigy *in vitro* testing and consider some of the disagreements between the parties with respect to the testing.

(a) *Cell-Free Inhibition*

[223] A cell-free assay is a test that demonstrates whether a compound will bind to and inhibit the target tyrosine kinase in the absence of the cell membrane.

[224] By April 1, 1993, only one of the Group 2 compounds – CGP 53716 – had been evaluated for its ability to inhibit cell-free PDGF-R protein kinase (Rönnstrand Report, TX 13, para 236). Dr. Heldin interpreted the test results, concluding that CGP 53716 has an IC_{50} value of "around 0.1µmol/litre" (Heldin Report, TX 71, paras 61-64).

[225] However, all six individually claimed Group 2 compounds inhibited v-ABL kinase in a cell-free test. The tests of five of the six individually claimed Group 2 compounds were reviewed by Dr. Rönnstrand in his report. He concluded that "[e]ach… exhibited inhibition of v-ABL with IC_{50} values in the micromolar range" (Rönnstrand Report, TX 13, para 237). The inhibition of v-ABL in a cell-free test by the remaining individually claimed Group 2 compound, CGP 53716, is noted by Dr. Van Etten (Van Etten Report, TX 37, para 150 referring to TX 55, Tab 2 at 11, 18). Dr. Rönnstrand agreed on cross-examination that a number of tests demonstrated cell-free v-ABL inhibition by CGP 53716, and these should have been included his report (4T781-782, 785, 788).

[226] Dr. Rönnstrand concluded that five of the individually claimed Group 2 compounds were tested against six distinct PKC isozymes. These Group 2 compounds did not inhibit the PKC isozymes tested at all or did so weakly (Rönnstrand Report, TX 13, paras 231-232). CGP 57010, the remaining individually claimed compound, was tested against at least one PKC isozyme, but may not have been tested against any others (TX 55, Tab 23).

[227] Ciba-Geigy also carried out a number of tests which showed not only the inhibitory properties but also the selectivity of Group 2 compounds.

1. All six of the individually claimed Group 2 compounds were tested against EGF-R kinase. The Group 2 compounds were "poor inhibitors" of EGF-R kinase (Rönnstrand Report, TX 13, paras 233-234).

2. Two of the Group 2 compounds were tested against phosphorylase protein kinase (PPK). These Group 2 compounds are "poor inhibitors" of PPK (Rönnstrand Report, TX 13, paras 233-234).

3. Two of the individually claimed Group 2 compounds were tested against protein kinase A (PKA). These Group 2 compounds are "poor inhibitors" of PKA (Rönnstrand Report, TX 13, paras 233-234).

[228] Thus, as of April 1, 1993, the Ciba-Geigy cell-free test results demonstrated that: (a) all six Group 2 compounds inhibited v-ABL; and (b) one of the Group 2 compounds inhibited PDGF-R. Although not all of the Group 2 compounds were tested against every known kinase, on the whole, the testing showed that the Group 2 compounds did not inhibit other kinases; in other words, they were selective inhibitors.

[229] Because only one Group 2 compound was tested against PDGF-R in a cell-free assay, I cannot conclude, on the basis of the cell-free testing alone, that the inhibition of that particular kinase had been demonstrated. However, as discussed in the following, Ciba-Geigy's whole cell tests are instructive and support a demonstrated inhibition.

(b) *Whole-cell Tests Directed to Inhibition*

[230] Another *in vitro* test – Western blot analysis – was used by the Ciba-Geigy researchers to determine whether the test compounds could enter intact cells and inhibit the relevant kinases

(Van Etten Report, TX 37, paras 117-119). In a Western Blot test, the researchers exposed the cells to an inhibitor and then measured the phosphorylation of PDGF-R kinase and v-ABL kinase, as compared to control cells. Two individually claimed Group 2 compounds, CGP 57148 and CGP 53716, were evaluated in Western Blot analysis (Rönnstrand Report, TX 13, para 247).

[231] Dr. Heldin described the Western Blots of these two compounds against PDGF-R kinase, concluding that they could cross the cell membrane and inhibit PDGF-R inside the cell (Heldin Report, TX 71, paras 72-74).

[232] During his oral testimony Dr. Rönnstrand took issue with the reliability of the Western Blot results for CGP 53716, which he believed were counter-intuitive, and was concerned about whether the experiment was repeated (Dr. Rönnstrand's testimony, 4T820-823). However, Dr. Rönnstrand acknowledged that CGP 53716 was tested in three other *in vitro* tests – the Northern blot test, the MAP kinase test and the ELISA test, also performed in cell culture. According to Dr. Heldin, in the MAP kinase test and the Northern blot test, CGP 53716 specifically inhibited the downstream signalling pathway of PDGF-R kinase, to the exclusion of other signalling pathways (Heldin Report, TX 71, paras 84-91). These tests therefore demonstrate that CGP 53716 may cross the cell membrane, selectively inhibit PDGF-R kinase and activate PDGF-R-mediated signalling. Dr. Rönnstrand himself acknowledged that CGP 53716 inhibited PDGF-R-induced *c-FOS* expression in his report (TX 13, para 252). Further, Dr. Rönnstrand admitted on cross-examination that he did not take into account the data from the MAP kinase test, as well as an ELISA test, an equivalent test to the Western Blot, which also measures enzyme inhibition inside cells (4T784, 810-811). Dr. Rönnstrand should have

considered the impugned Western Blot test in the context of the other testing performed on CGP 53716, including the ELISA testing, the Northern blot testing and the MAP kinase testing.

[233] In the case of CGP 53716, where other successful tests were carried out, the inconclusive Western Blot test does not establish the inutility of that compound.

[234] With respect to the Western Blot tests conducted against v-ABL, Dr. Rönnstrand concluded that CGP 53716 exhibited a positive result, but CGP 57148 did not inhibit v-ABL in this cell line (Rönnstrand Report, TX 13, paras 249-250; T 483-484, 863-865). However, Dr. Rönnstrand admitted that the Western Blots relating to CGP 57148 were difficult to read, due to overexposure and lack of molecular weight markers (Rönnstrand Report, TX 13, paras 248-250; 4T804-805, 868; see also Dr. Van Etten at 8T1650-1651). Nothing should be read into this inconclusive test of CGP 57148.

[235] Similar to Western Blot analysis, ELISA assays also measure enzyme inhibition in intact cells (Van Etten Report, TX 37 at para 126). Dr. Van Etten reviewed three ELISA tests relating to CGP 57148, concluding that this compound was "highly effective" in its inhibition of PDGF-R kinase inside an intact cell (Van Etten Report, TX 37, paras 125-127). The documents that Dr. Etten reviewed demonstrate that the other five individually claimed Group 2 compounds were also tested and demonstrated similar levels of inhibition (Selection of *in vitro* testing, TX19, Tabs 12-16; see also TX 55, Tab 23).

(c) *Anti-proliferation Tests*

[236] Ciba-Geigy also conducted cell culture assays measuring the ability of the tested compounds to prevent or slow the growth of malignant cells (Heldin Report, TX 71, paras 79-91; Rönnstrand Report, TX 13, para 244; Van Etten Report, TX 37, paras 121-122).

[237] One set of experiments measured the ability of four individually claimed Group 2 compounds to inhibit the growth a BALB/c 3T3 *v-SIS* cell line (Rönnstrand Report, TX 13 at paras 241, 244-245). Dr. Rönnstrand concluded that these four compounds "strongly inhibited cell proliferation"; given the overexpression of PDGF by this cell line, this result was suggestive of inhibition of cell proliferation through the inhibition of PDGF-R.

[238] The Ciba-Geigy researchers conducted a second set of experiments to measure inhibition by CGP 53716 of v-ABL-dependent cell proliferation. The Plaintiffs submit that these tests failed, thereby demonstrating the inutility of that compound. I do not agree with the Plaintiffs' characterization of these experiments as "failed". At best, these studies may be inconclusive because the cell line was not truly v-ABL dependent. Dr. Rönnstrand merely commented that any positive results would not be determinative, since further experimentation would be required to demonstrate that inhibition of cell proliferation was mediated through inhibition of v-ABL kinase (Rönnstrand Report. TX 13, paras, 240, 246). Dr. Van Etten stated that this was a flawed test because it of "a technical reason" or because "the cell line they used was not truly ABL dependent" (Van Etten, 8T1654, 1658-1661, 9T1698; see also Dr. Lydon's similar remarks, 10T2010-2017, 2070, 2095). Dr. Van Etten also noted that in a 1996 paper by the PK Group, a

different cell line was used, although the old cell line was referenced in respect of other tests (9T1736-1739; TX 46). Lastly, these experiments were ignored by the Ciba-Geigy researchers in their summary report relating to CGP 53716, indicating that the researchers did not place much weight on them (Novartis Reports, TX 55, Tab 2). Since the majority of the evidence suggests that the impugned cell line is not v-ABL-dependent, the Plaintiffs have not met their burden to demonstrate that this experiment reveals lack of utility on a balance of probabilities.

(d) *Other in vitro Testing Directed to Selectivity*

[239] In addition to certain of the cell-free tests described above, the researchers at Ciba-Geigy conducted a number of other tests to establish the selectivity of the claimed compounds.

[240] One such test was a MAP kinase test. MAP kinase is a protein that is activated by the PDGF-R signalling pathway. When MAP kinase is activated, it transmits signals from PDGF-R kinase to the nucleus of the cell, which regulates cell growth (Heldin Report, TX 71, paras 52, 84). The purpose of the MAP kinase tests conducted by Ciba-Geigy was to determine if MAP kinase activation induced by an inhibitor selectively occurs through a particular pathway – in this case, the activation of PDGF-R by its ligand, PDGF. Dr. Heldin concluded that CGP 53716 inhibits MAP kinase activation induced by PDGF, but not MAP kinase activation induced by three other molecules (Heldin Report, TX 71, paras 84-85).

[241] The researchers also conducted Northern Blot tests to determine the amount of messenger RNA transcribed from the *c-FOS* gene as a measure of gene expression induced by PDGF-R

signalling (Heldin Report, TX 71 at paras 52, 86-91; Dr. Rönnstrand's testimony at 3T480-481). Messenger RNA is transcribed from genes and transported outside the nucleus where it is used to build proteins. *c-FOS* is a gene that governs cell growth and proliferation, the expression of which is induced by PDGF-R signalling.

[242] The *c-FOS* assays are significant because they demonstrate selective inhibition of the downstream PDGF-R signalling pathway without testing against all kinases (Heldin Report, TX 71, para 91; Dr. Heldin's testimony, 13T2640-2641; Dr. Lydon's testimony, 10T1987-1988, 1991-1992, 2007-2008; Dr. Zimmermann's testimony, 12T2423-2426). Even Dr. Rönnstrand concluded from this experiment that both CGP 53716 and CGP 57148 inhibited PDGF-induced expression of *c-FOS* (Rönnstrand Report, TX 13 at para 252; 3T485).

(e) *Summary on the Testing of the Group 2 Compounds*

[243] When evaluating the Group 2 compounds to determine whether or not they inhibit v-ABL in a cell-free test, Dr. Rönnstrand perhaps best summarized the Ciba-Geigy testing, at paragraphs 237-238 of his report (TX 13):

> A review of the Novartis Documents reveals that, by April 1, 1993, Ciba-Geigy had evaluated six Group 2 compounds for their ability to inhibit cell-free v-Abl protein kinase (CGP 53714 [ND 94], 57010 [ND 94], 57011 [ND 94 and 95], 57012 [ND 94], 57014 [ND 94 and 95], and 57148 [ND 94 and 95]). Each of these six compounds exhibited inhibition of v-Abl with IC50 values in the micromolar range.

[244] This statement, taken together with Dr. Rönnstrand's acknowledgments of the testing of CGP 53716 on cross-examination, demonstrates that all six individually claimed Group 2

compounds inhibited v-ABL kinase in a cell-free test. Moreover, the evidence is clear that selectivity was demonstrated through a number of tests of the compounds against other kinases (such as PKC).

[245] Therefore, as of April 1, 1993, in my opinion, Novartis had demonstrated that imatinib and five other individually claimed compounds (all of which belong to Group 2) selectively inhibited v-ABL protein kinase in an *in vitro* assay. Given the promise of these claims of inhibition of either PDGF-R or ABL, the utility of Claims 28 to 33 had been demonstrated.

[246] In the event that I am wrong and the compound claims promise that each of the Group 2 compounds will inhibit both ABL and PDGF-R kinases, I turn to the evidence related to PDGF-R inhibition. By April 1, 1993, only one Group 2 compound had been tested for PDGF-R inhibition in a cell-free assay. However, other *in vitro* tests were carried out on the remaining compounds. All of the individually claimed Group 2 compounds were tested for inhibition of PDGF-R in the ELISA test. Dr. Rönnstrand admitted that he should not have overlooked this test. Moreover, four Group 2 compounds strongly inhibited cell proliferation in the anti-proliferation test. Selectivity for the PDGF-R signalling pathway was demonstrated through the testing of CGP 53716 in the MAP kinase test, as well as the testing of CGP 57148 and CGP 53716 in the Northern Blot tests. Cumulatively, the testing amply demonstrated the utility of the Group 2 compounds as selective inhibitors of PDGF-R. Accordingly, even if the patent promises that each of these six compounds will selectively inhibit both PDGF-R and ABL kinases, utility has been demonstrated.

[247] Similar evidence before me shows that the testing carried out by Ciba-Geigy demonstrated the utility of the specifically claimed Group 1 compounds (Claims 9 to 27 and 34 to 39). On the basis of Dr. Rönnstrand's analysis, the Plaintiffs appear to acknowledge that 11 Group 1 compounds were tested against one or more PKC isozymes and found to inhibit PKC. Many of these compounds were tested against PKA and EGF-R (and a few were also tested against PPK) and they were found to inhibit these enzymes only at far higher concentrations, indicating selectivity. The utility of the Group 1 compounds has also been demonstrated.

B. *Utility of Claims 1, 2, 3, 4, 5 and 7*

[248] Claims 1 to 8 of the '203 Patent follow the format of many pharmaceutical patents with "cascading claims". Claim 1 is to "billions" of compounds. The claims become progressively more focussed as they descend. Of particular interest are Claims 5 and 7. Obviously, Ciba-Geigy did not test all of the compounds of formula I (Claim 1) or of the other broader claims and any utility would have to depend on sound prediction. The question arises as to whether one can reasonably extrapolate from the individually claimed compounds demonstrated to be selective kinase inhibitors to the classes of compounds included in the more general claims. In certain circumstances, the Federal Court has recognized that the utility of certain untested compounds may be soundly predicted on the basis of the information and science that was available at the filing date (see, for example, *Perindopril*, above at para 345).

[249] Claims 6 and 8 are broad claims encompassing compounds that, due to their chemical structures, do not include imatinib. Neither the parties nor the experts considered any of these claims. Neither will I.

[250] The important question where there are general claims – such as is the case with the '203 Patent – is whether it is reasonable to predict, on the basis of a few examples, that all of the compounds of the general claim will operate in a similar fashion. The possibility of extrapolating specific test results to a more general claim is a subject where I was grateful for the assistance of experts in the area of medicinal chemistry. This is where Drs. Heathcock and Wuest were very helpful.

[251] During cross-examination, Dr. Heathcock explained, in very easy-to-understand words, how a medicinal chemist looks at the interaction of inhibitors and enzymes and comes to extrapolate test results from one tested compound to a class of compounds (5T997-998):

> Well, the key in the lock is the way that the – that most medicinal chemists think of enzymes. The enzyme is the lock and the key has to fit into the lock just right and that's why you want all of those little bumps to fit there in the inside.
>
> And then the variable part – when you find a series of drugs where you can vary one part a lot, that's usually assumed that that is in the handle of the key, right? It's got a flap on the outside and it may help to bind the key to the outside of the door or it may help to carry it around in the body or something like that, but it's not – you can play around with that part without affecting the actual teeth of the key. [Emphasis added.]

[252] This notion of "key in the lock" is the basis upon which a particular compound (or, where appropriate, a class of compounds), even if not tested, can be found to have utility on the basis of

sound prediction. Of course, it is self-evident that, to rely on this theory, one must examine the structures and the likely chemical reactions.

[253] In more technical terms, Dr. Wuest explained (TX 53, paras 81-82) how reasonable extrapolations from the specific compounds tested to the more general class claims of the '203 Patent would be made by a medicinal chemist.

> . . . I think it is factually correct that certain compounds with lower alkyl substituents were not made. Indeed, only methyl substituents appear to have been made for R_4 and R_8. Nevertheless, if the role of the alkyl substituents is to subtly alter the molecular shape, in part by favoring a specific conformation different from that favored when R_4 and R_8 are both hydrogen, then a chemist would recognize that methyl groups and other lower alkyl substituents are likely to have similar effects. As expressed in the '203 Patent, compounds in which R_4 and R_8 are hydrogen are PKC inhibitors, and compounds in which one of R_4 and R_8 is a lower alkyl (e. g. a methyl group) are PDGF-receptor and abl-tyrosine kinase inhibitors. It is clear that at least 22 compounds were made where R_4 and R_8 are hydrogen, and at least 7 compounds were made where R_4 or R_8 is methyl. Those in the first group inhibit PKC, and those in the second group inhibit PDGF-receptor and abl-tyrosine kinases. From these facts, it is a relatively simple extrapolation to infer that other lower alkyls would function in a similar manner. Consequently, relatively few substituents would need to be considered. Indeed, many pairs of compounds in the examples of the '203 Patent [differ] only in the substitution at R_4 and R_8, and the other parts of the molecules are otherwise identical. The different behaviors as kinase inhibitors, despite the overall molecular similarity, are consistent with the notion that the methyl substituent induces a change in shape and that other lower alkyl substituents would be likely to show similar behavior.
>
> For full confirmation, experiments would have to be done, of course, but the basic structural inference is one that chemists are trained to make. Such plausible inferences have been made in countless patents that have issued. [Emphasis added.]

[254] Dr. Heathcock was asked to look at the relevant class claims and to:

> [D]iscuss the scope and the breadth of claims 1 to 5 and 7 of the '203 patent in comparison to the compounds made and tested by Novartis prior to April 1, 1993 in the Novartis Documents. (TX 22, para 19)

[255] In his report (TX 22, para 52), Dr. Heathcock opined that:

> In light of Formula I and the possible substituents at each position (R_1 to R_{10}), it is readily apparent that claim 1 encompasses a vast number of compounds. Indeed, based on my estimation, there are many billions of compounds encompassed within the scope of claim 1. The substituents at positions R_1 to R_{10} vary significantly in terms of their characteristics, including size, shape, polarity, and hydrophilicity/hydrophobicity. The skilled person would understand that each of these characteristics can have a significant impact on whether a compound can bind to the active site of an enzyme. [references omitted]

[256] Dr. Heathcock examined and explained the chemical differences between those compounds tested and the billions of variants possible with Claim 1. He concluded that:

> [T]he structural diversity of the 29 compounds made and tested was very limited in comparison to the breadth of the possible chemical substituents… [T]here was no way for the inventor (or anyone else) to know how all of the substituents on the compounds that were not made and tested would affect the resulting activity of the compounds.
> (TX 22, para 68)

In other words, Dr. Heathcock's opinion was that selective inhibition activity of all of the Claim 1 compounds could not be predicted from the compounds tested in the Ciba-Geigy laboratories. Dr. Heathcock carried out a similar analysis for Claims 2, 3, and 4 and reached similar conclusions. In these conclusions, he was not seriously challenged. It follows that we cannot extrapolate from the efficacy of the tested compounds to conclude that all of the compounds of Claims 1, 2, 3 and 4 have the utility promised by the '203 Patent.

[257] The situation for Claims 5 and 7 is different. Dr. Heathcock, in his report (TX 22, para 71) stated as follows:

> Likewise, claim 5, while even more limited than claim 4, still provides for a very broad selection of chemical substituents at position R_{10} such that the inventor (or anyone else) could not have made a reliable prediction of the activity of all of the compounds within the scope of that claim. Although claim 5 does not include some of the more extensive definitions of substituents at position R_{10} that are included in claims 1 to 4 and claim 7, claim 5 still includes substituents well beyond any examples that were prepared and tested, and does not limit the combination of these unprecedented substituents. For example, even claim 5 includes the following example, which a person of ordinary skill in the art would recognize has virtually no chance as an *in vivo* kinase inhibitor due to its strong hydrophobicity (poor water solubility). [Emphasis added.]

[258] The problem with Dr. Heathcock's opinion on Claim 5 is that he was looking for evidence that the compounds would be potential *in vivo* inhibitors. That utility goes beyond the promise of the compound claims. So long as the compounds can exhibit *in vitro* selective inhibition – or can be soundly predicted to do so – they will have utility.

[259] During cross-examination, Dr. Heathcock acknowledged that all 29 compounds made and tested by Ciba-Geigy are included in Claim 5 (5T1093). In the discussion with counsel for Novartis that followed, Dr. Heathcock examined all of the possible substituents for R_1 to R_{10} in the Claim 5 compounds and related these to the tested compounds (5T1095-1107). Counsel for Novartis posed the following question to Dr. Heathcock:

> So when we look at the scope of Claim 5 and compare with the 29 compounds, the inventors, the Ciba-Geigy researchers had explored each of these alternatives that are set out here, hadn't they? (5T1107)

[260] After considerable further discussion, Dr. Heathcock summarized his position on Claim 5 as follows:

> Oh, I see what you are saying so, yes, okay. So they did a – they did a reasonably good job of scoping out the conditions that were left to be variable.
>
> My objection with – I don't have a really strong objection to 5. I think they went beyond their comfort zone with permitting, you know, structures of the sort that I illustrated.
>
> We – I think I have it on paragraph 61 of my report, you know, where you could have several alkyl groups that would make the compounds more lipophilic than I believe a medicinal chemist would be comfortable with. But the claim 5 would make a respectful Claim 1. (5T1108-1109)

[261] In his report, Dr. Heathcock describes Claim 7 as a "slightly more restrictive claim to the Group 2 compounds" (TX 22, para 73) and concluded that the activity of the compounds of Claim 7 could not be predicted for the same reasons as he expressed for Claim 5. However, his opinions during cross-examination should be taken into account. Since Claim 7, read dependent on Claim 5, would include an even narrower class of compounds than Claim 5, it appears that Dr. Heathcock now accepts that the compounds of either Claim 5 or 7 could be reasonably predicted to exhibit the same properties as those of the tested compounds.

[262] This understanding of Claim 7 is consistent with that of Dr. Wuest. Dr. Wuest read Claim 7 as dependent on Claim 5, and observed (TX 53, paras 93-95) that "virtually all aspects of claim 5 are illustrated by examples to provide support for the scope claimed". As such, he was of the view that, in Claim 7:

> . . . there is good representation of the claimed compounds in the form of concrete examples. Because many examples were made, it

> would be reasonable to infer that the compounds would have similar inhibitory activity. [Emphasis added.] (TX 53, para 95)

[263] In sum, I conclude that it is a reasonable inference that any compound of Claims 5 or 7 would be likely to exhibit the same inhibitory characteristics as the tested compounds. Thus, the final opinions of both Dr. Heathcock, as adjusted during cross-examination, and Dr. Wuest provide support for a finding that selective inhibition of protein kinases (dependent on whether the compound belongs to Group 1 or Group 2) is soundly predicted for all of the compounds of both Claim 5 and Claim 7.

C. *Conclusion on the Utility of the Compound Claims*

[264] On the issue of the utility of the compound claims of the '203 Patent, I conclude that, as of April 1, 1993:

1. The utility of the compounds of Claims 9 to 27 and 34 to 39 as selective inhibitors of PKC and of Claims 28 to 33 as selective inhibitors of ABL or PDGF-R had been demonstrated as of April 1, 1993;

2. The utility of Claims 5 and 7 as selective inhibitors could be soundly predicted as of April 1, 1993; and

3. The utility of all of the compounds of Claims 1, 2, 3 and 4 had neither been demonstrated nor soundly predicted.

[265] It follows that the utility of Claim 44 – a claim to the process for making these useful compounds – has also been established.

IX. Utility of the Use Claims

[266] For the use claims (Claims 45 to 48), the promise is that a compound included in Claims 1 to 39 can be used to treat the diseases or conditions specified in the use claims. There is no question in my mind that demonstration of such utility would require more than the *in vitro* testing that was carried out in the Ciba-Geigy laboratories. Even though the state of the art, as discussed below, had drawn some strong inferences of the link between inhibition of the v-ABL kinase and CML, that link had not, as of April 1, 1993, been demonstrated. Thus, I must consider the question of sound prediction.

[267] It is important to repeat that the Plaintiffs bear the burden on this issue of validity. To demonstrate lack of utility, they must show "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" (*Consolboard*, above at 525-526). More specifically related to the question of sound prediction, a party challenging the utility of a patent based on sound prediction must demonstrate that the prediction was not sound or that there is evidence of a lack of utility. As stated in *AZT*, above at paragraph 56:

> If a patent sought to be supported on the basis of sound prediction is subsequently challenged, the challenge will succeed if, *per* Pigeon J. in *Monsanto Co. v. Commissioner of Patents*, [1979] 2 S.C.R. 1108, at p. 1117, the prediction at the date of application was not sound, or, irrespective of the soundness of the prediction,

> "[t]here is evidence of lack of utility in respect of some of the area covered".

[268] The focus of all of the evidence and argument in the trial was with respect to Claim 46 when read together with Claim 29. As I have concluded earlier in these reasons, Claim 46 when read together with Claim 29, promises that imatinib: (a) will inhibit PDGF-R or ABL kinases; and (b) will have the potential to treat tumours in warm-blooded animals. We know that imatinib (Claim 29) had demonstrated inhibition of ABL kinase. Thus, stated in terms of utility, as of April 1, 1993, could the use of imatinib (Claim 29) for the "chemotherapy of tumours" (Claim 46) be soundly predicted? That is the question I will address.

[269] As set out earlier in these reasons, a sound prediction of utility requires that the evidence show:

1. a factual basis for the prediction;

2. an articulable and sound line of reasoning connecting the desired result and the factual basis; and

3. disclosure of the factual basis and line of reasoning in the patent.

[270] I will consider each of these requirements in the context of Claim 46 when read together with Claim 29. Some of the testing discussed also relates to Claim 46 as read with the other individually claimed compounds.

A. *Factual Basis*

[271] The question of sound prediction is one of fact (*AZT*, above at para 71). The inventors must be able to show that, at the relevant time, they were in possession of a factual basis upon which they could articulate the desired result. The perspective being examined at this stage is a subjective one. The knowledge, activities and endeavours of the inventors themselves must be considered (*Merck & Co v Apotex Inc*, 2010 FC 1265 at para 498, 91 CPR (4th) 1 [*Lovastatin (FC)*], aff'd 2011 FCA 363, 102 CPR (4th) 9).

[272] Ciba-Geigy's interest in selective kinase inhibitors began in the mid-1980s. As the general interest in the field increased, so too did Ciba-Geigy's work in the area. An overview of the PK Group and its achievements is set out in the Background section of these reasons. Three of the scientists with direct knowledge of the Ciba-Geigy research throughout the period from 1985 to 1993 – Dr. Zimmermann, the inventor, Dr. Lydon and Dr. Fabbro – described their knowledge, activities and endeavours. There is no dispute that the result of their efforts was a novel class of compounds that could selectively inhibit certain kinases. However, at this stage of my analysis, the broad question is whether they had a factual basis for predicting the *in vivo* efficacy of the compounds in the treatment of tumours (Claims 46 and 47) and atherosclerosis (Claims 45 and 48). With respect to the narrow issue of Claim 46 when read with Claim 29, did the Ciba-Geigy scientists have a factual basis to predict that imatinib would have utility in the chemotherapy of tumours?

[273] I have already thoroughly discussed the evidence upon which I have concluded that the compounds of Group 2 had demonstrated utility in that they had all shown selective inhibition *in vitro*. This is the essential part of the factual basis of the sound prediction that these compounds (in particular imatinib) could be useful in the chemotherapy of tumours and it is reflected in the *in vitro* studies disclosed in the '203 Patent.

[274] At this stage of my analysis, I turn to the *in vivo* testing that was done in the Ciba-Geigy laboratories. The Plaintiffs submit that Ciba-Geigy did not carry out enough testing to obtain a sound prediction that the compounds of the '203 Patent meet the promise of *in vivo* therapeutic effects on tumours associated with PDGF-R and ABL kinases. They also assert that the testing that was done demonstrates that the compounds lack utility in this regard. An immediate problem with the position of the Plaintiffs on this question is that I have determined that the promise does not require therapeutic effects on tumours associated with both PDGF-R and ABL; rather the promise is met if the compound can treat tumours associated with PDGF-R or ABL.

[275] To assess the extent of Ciba-Geigy's factual basis, I review the *in vivo* testing that was carried out. *In vivo* testing was conducted to determine whether Ciba-Geigy's inhibitors could reduce tumour size in a mouse (Heldin Report, TX 71, para 92). The test subjects were mainly nude mice, which have a deteriorated or absent thymus. These mice are unable to generate T cells and therefore have a severely defective immune system (Rönnstrand Report, TX 13, para 129).

[276] Dr. Rönnstrand was generally dismissive of the use of nude mice to test the efficacy of the claimed compounds. In response to this criticism, Dr. Van Etten explained that use of immunocompromised mice is acceptable as long as the immune system does not play a role in the response to the tumour (9T1708). I had no evidence that the immune system played a role in the tumour response. I accept that the use of nude mice in testing is a viable way of assessing the efficacy of tested compounds in warm-blooded mammals.

(1) PDGF-R related Tumours

[277] I begin with the *in vivo* tests carried out with respect to tumours dependent on PDGF-R kinase. Four individually claimed Group 2 compounds were tested in nude mice injected with 3T3 *v-SIS* fibroblast cells, transfected with a gene that causes overexpression of the PDGF ligand (Rönnstrand Report, TX 13, paras 134-136). Dr. Rönnstrand acknowledged that the assays generally indicated slowing of the growth of the tumour (Rönnstrand Report, TX 13, para 136). This is a positive result.

[278] However, Dr. Rönnstrand, in addition to his problem with the use of nude mice, was concerned that: (a) treatment was started within one day of implanting the tumour, which did not give the tumour cells sufficient time to grow and establish themselves; and (b) the fibroblast cells changed after they were cultured and are no longer representative of human cells (Rönnstrand Report, TX 13, paras 135, 141-144, 259-260; 3T573-574). Viewed in the context of the patent, the state of the art and the evidence of the other two experts, it appears that Dr. Rönnstrand was looking for certainty that is not required to demonstrate a sound prediction.

[279] Dr. Heldin and Dr. Van Etten acknowledged limitations to experiments conducted in mouse models, and that predictions about the treatment of humans cannot be based on such studies with absolute certainty (9T1705-1707, 13T2659-2660). However, both experts concluded that, despite the timing when treatment began and the cells used, these experiments demonstrated a relevant reduction in tumour growth (Van Etten Report, TX 37, paras 134-138; Heldin Report, TX 71, para 149).

[280] In particular, Dr. Heldin acknowledged Dr. Rönnstrand's criticism relating to the start of treatment within one day of implanting the tumour (Heldin Report, TX 71, para 198). Dr. Heldin noted that prophylactic treatment of this kind would comprise chemotherapy of tumours within the contemplation of Claim 46.

[281] The change in the fibroblast cells was adequately explained by Dr. Van Etten. Although the fibroblast cells had changed because of genetic drift, many changes in the fibroblasts were necessary so that they have the properties of cancer cells to enable their use in the experiment in the first place (9T1711-1713). Further, Dr. Van Etten confirmed that these fibroblast cells maintained the features of their origin.

[282] A comparison of Dr. Rönnstrand's evidence with that of Dr. Heldin and Dr. Van Etten demonstrates Dr. Rönnstrand's misunderstanding of the concept of sound prediction. Both Dr. Heldin and Dr. Van Etten acknowledged the limitations of the nude mice that were tested. However, with a mind willing to understand, they took into account whether these experiments demonstrated certainty of *in vivo* treatment or a reasonable inference of utility. However,

Dr. Rönnstrand appeared to require certainty and it is unclear if any animal model would provide sufficient certainty for him. During his testimony, Dr. Rönnstrand stated that even a "a very good experimental system" is just a model that does not necessarily reflect a human disease state (3T573-574). Further, in his report, Dr. Rönnstrand appears to raise questions without considering whether any reasonable inferences may be made (TX 13, paras 259-263). This misunderstanding of the concept of sound prediction, which does not require certainty (*AZT*, above at para 76), means that Dr. Rönnstrand's evidence on this point is of limited usefulness. I therefore prefer the testimony of Drs. Heldin and Van Etten.

(2) ABL-related Tumours

[283] Only one compound – CGP 53716 – was tested *in vivo* against v-ABL. The Plaintiffs point to this *in vivo* experiment, arguing that this experiment "failed" thereby showing that the prediction was unsound. I do not agree.

[284] The experiment in question tested CGP 53716 in nude mice injected with BALB/c AMulV fibroblast cells to determine whether the compound inhibited the growth of ABL-related tumours (Rönnstrand Report, TX 13, para 137). Dr. Rönnstrand initially interpreted this experiment as a failed test, stating in his report that, "no statistically significant effect on tumour growth was observed" (Rönnstrand Report, TX 13, paras 137-139 referring to Exhibit 20, Tab 2; 3T463-467). He suggested that this result is not caused by a solubility problem, since CGP 53716 showed inhibition in the PDGF-R *in vivo* assay described above.

[285] On the other hand, Dr. Van Etten and Dr. Lydon testified about a solubility problem concerning this particular formulation of CGP 53716 (10T2020-2021; 8T1559-1560). Dr. Van Etten explained that the effective concentration of CGP 53716 was too low to observe any effect in this experiment, whereas a positive result was observed against PDGF-R because CGP 53716 was more potent against this kinase (Van Etten Report, TX 37, paras 149-150; 8T1557-1559). Further, Dr. Lydon pointed out the attempts of the PK Group to address the solubility problem; at least one of the PDGF-R nude mouse experiments employed a surfactant, tween 80, to improve the bioavailability of CGP 53716 (10T2090).

[286] On cross-examination, Dr. Rönnstrand appeared to be in agreement with Drs. Van Etten and Lydon. He agreed that CGP 53716 is a better inhibitor of PDGF-R kinase than ABL kinase. Further, he appeared to acknowledge that this *in vivo* experiment should be given no weight since the reagents were in suspension (4T828-829, 842-843). Although the Plaintiffs characterize the exchange between Dr. Rönnstrand and counsel for Novartis as a reiteration that the compound failed, and not the experiment, the transcript reveals otherwise. Counsel for Novartis clearly asked Dr. Rönnstrand whether no weight should be put on the experiment and whether the experiment failed, and Dr. Rönnstrand agreed:

> A: If I do an experiment in the lab, I want to have a solution. I would never do a solution where the compound is not dissolved. Then I know I cannot have any control over the concentration if it is in a suspension. It would do this in solutions.
>
> Q: So if it is in the form of a suspension, you would put no weight on the results. Is that what you are telling me?
>
> A: I would not do a scientific experiment where the reagents are in suspension. There is big problems where there is risk of sedimentation and many things.

Q: So we really shouldn't put any weight on the experiment in 250. All right. Failed experiment?

A: Yes, obviously.

[287] Therefore, the evidence of both Dr. Rönnstrand and Dr. Van Etten demonstrates, on a balance of probabilities, that this *in vivo* experiment failed because of a solubility problem and not because CGP 53716 was a poor inhibitor. A failed experiment is far different from an experiment that shows that a compound fails to do what it is expected to do. Therefore, on the basis of this experiment, the Plaintiffs have not demonstrated that CGP 53716 lacks the utility promised by the Claim 46 when read with Claim 28.

(3) Maximum Tolerated Dose

[288] One issue that arises in drug development is the ability of a drug to be tolerated; a drug that is toxic at levels that would be therapeutic is obviously not a good choice for further development. As of April 1, 1993, the compounds of the '203 Patent were far from the stage at which clinical trials could be commenced. Nevertheless, to give themselves some indication, compounds CGP 53716 and CGP 57148 were subjected to a maximum tolerated dose test, in which researchers administered large amounts of a test compound to mice to identify a lethal dose (Heldin Report, TX 71, paras 96-98; 13T2621-2624). Dr. Heldin concluded that the mice tolerated large amounts of both CGP 53716 and CGP 57148. This is a fair – albeit not conclusive – predictor that toxicity will not be a serious deterrent to therapeutic use in warm-blooded animals.

[289] I observe that the toxicity testing was limited at this stage and is not necessary for a sound prediction. However, it is important to note that the researchers were not at the stage of final trials; indeed, they were still unsure as to which of the Group 2 compounds would ultimately be pursued as drugs. This test, had it been negative (that is, shown toxicity at low doses), would almost certainly have indicated that these two compounds (and, by extrapolation, all of the other Group 2 compounds) would not live up to the promise of the use claims in the '203 Patent. However, the tests were successful, thereby providing further support to the sound prediction.

(4) Summary on Factual Basis

[290] In summary on the question of factual basis, all of the Ciba-Geigy tests pointed to a conclusion that the Group 2 compounds – including imatinib – would be useful in treating tumours in warm-blooded animals. Although a few tests may have been inconclusive, not a single test demonstrated a negative result. I am satisfied that the Ciba-Geigy researchers had a factual basis for predicting the utility of the Group 2 compounds in the chemotherapy of tumours.

B. *Articulable Line of Reasoning*

[291] I next consider whether the Plaintiffs have shown that there was no articulable line of reasoning from which the desired results could be inferred from the factual basis.

[292] Much of the evidence before me with respect to the use of these compounds related to the prior art – the common general knowledge of scientists working in the field. Every skilled person brings to the reading of a patent his knowledge of the field in which the patent operates. The person of ordinary skill in the art would be expected to bring to his reading of the patent a foundation of common general knowledge that would enable him or her to understand and practise the patent. In *Latanoprost,* the Court of Appeal acknowledged that expert evidence relating to the knowledge of the skilled person might bridge the gap between the factual basis disclosed in the patent and the prediction of the inventor (*Latanoprost*, above at paras 45-47). In that case, however, the court concluded that none of the experts could point to anything in the patent that could provide a line of reasoning and the prior art described by the experts contradicted the prediction.

[293] The court's conclusion in *Latanoprost* leads me to acknowledge that I must be cautious in the use of prior art to bridge the gap between experimental results and sound prediction. The question is: given the experimentation and laboratory results that formed the factual basis for the invention of imatinib (Claim 29), could Novartis reasonably infer that imatinib would have utility for the chemotherapy of tumours (Claim 46)? If there is a "gap", can this gap be bridged by the prior art?

[294] In this section of the reasons, I summarize what I believe was the general common knowledge of our hypothetical skilled person. This knowledge was indeed "general" in that it was generally and widely known to persons working in the field. Once again, the experts were extremely helpful and, except where noted and analyzed, did not disagree.

(1) Protein Kinases and Hyperproliferative Disorders

[295] As already observed, the essence of the ‘203 Patent is selective inhibition of particular protein kinases. The development of inhibitors of protein kinases was an active area of research for drug companies at the time the ‘203 Patent was filed (Dr. Rönnstrand, 4T635-636, 642-644). Researchers knew that various hyperproliferative diseases, such as cancer, could be treated through interference with kinase signalling (Heldin Report, TX 71, paras 57-59; Dr. Rönnstrand, 4T635-636, 642-644).

[296] One of the clearer affirmations of the link between inhibition of protein kinases and therapeutic treatment of cancers was provided by Dr. Rönnstrand (4T642-643):

> I have nothing, no problem, with the idea that one should have pharmaceutical intervention with the growth factor signaling pathways in order to cure or treat cancer with kinase inhibitor or other inhibitors. I think that’s a perfectly sound and valid idea at that time [April 1993] and today.

(a) *ABL Kinase and CML*

[297] Of critical importance, Dr. Van Etten, Dr. Heldin and Dr. Rönnstrand acknowledged that a skilled person would be aware of the causative role that BCR-ABL plays in CML.

[298] By April 1, 1993, researchers had thoroughly investigated the connection between BCR-ABL kinase and CML (Van Etten Report, TX 37, paras 49-70; 8T1513-1516). For example:

- In 1960, Nowell and Hungerford first observed the Ph chromosome in leukemic cells from patients with CML.

- Later on, the Ph chromosome was found to be a fusion gene, *BCR-ABL*, which encodes a tyrosine kinase with increased activity in comparison with its normal counterpart, c-ABL.

- Introduction of *BCR-ABL* into mouse stem cells led to pathologies analogous to CML. Researchers demonstrated, using Koch's postulates, that BCR-ABL was both necessary and sufficient to cause CML-like leukemia in mice.

- Inhibition of the expression of *BCR-ABL* using anti-sense DNA selectively slowed the growth of CML precursor cells.

- Inhibition of the BCR-ABL fusion protein using non-selective inhibitors decreased proliferation and survival of CML patient cells and cells expressing *BCR-ABL*.

[299] On the basis of these studies, Dr. Heldin and Dr. Van Etten asserted that it was known in 1993 that BCR-ABL was the direct cause of CML (Van Etten Report, TX 37, para 70; Heldin Report, TX 71, paras 54, 57; 13T2609). Even Dr. Rönnstrand agreed that development of a cancer treatment to target CML was a good choice because it was a simple, well-understood cancer dependent on a single pathway (3T611-613). Dr. Rönnstrand acknowledged that BCR-ABL kinase directly caused CML, stating that the studies conducted by 1993 demonstrated "really conclusive evidence" (4T705-711).

(b) *Inhibitors of v-ABL and BCR-ABL*

[300] The Plaintiffs argue that there was no evidence that the inhibition of v-ABL kinase would translate to inhibition of BCR-ABL kinase. Dr. Rönnstrand opined that it was unknown in 1993 whether an inhibitor v-ABL would also inhibit BCR-ABL. Thus, the Plaintiffs assert, there is a fatal break in the line of reasoning between imatinib and CML treatment.

[301] I agree that there was no certainty, in 1993, that a link between v-ABL and BCR-ABL existed. However, as explained by Drs. Van Etten and Heldin, the similarity of the two molecules was well known at this time. Dr. Van Etten explained the similarity between v-ABL and BCR-ABL as follows:

Q. And in that paragraph 54 you also refer to BCR-ABL?

A. Yes.

Q. How does that relate to the v-ABL that we're talking about?

> A. So BCR ABL is a fusion of human c-ABL with this protein called BCR. And it includes almost all of c-ABL in that fusion, just the very, very first part of it is gone – really just 25 or 20 amino acids or so. So the part of ABL that's there, including the entire end of ABL, including all of that kinase domain or catalytic domain. So that's identical to c-ABL, which is very close to mouse ABL, which is identical to v-ABL. So that is how they stack up. In that portion of the protein between v-ABL, mouse c-ABL, human c-ABL and BCR-ABL, [there are] three amino acid differences.
>
> Q. So what did that tell researchers at the time as to the value of v-ABL in assays?
>
> A. . . .
>
> What I told them was that they expected that the physiologic effects of expressing ABL in the effects of inhibitors on different forms of ABL would be similar between v-ABL and BCR-ABL. And, in fact, turned out to be true. I know of no compounds, then or now, that have a different effect on v-ABL and BCR-ABL.[Emphasis added.] (8T1500-1501)

[302] Similarly, Dr. Heldin stated that a skilled person could not assume that inhibition of BCR-ABL was a certainty given inhibition v-ABL; however, this was a reasonable hypothesis given what was known in 1993 about the similarity of these two proteins.

[303] Dr. Rönnstrand appears to base his opinion on a paper published in 1992, in which it was noted that certain compounds inhibited v-ABL but not BCR-ABL and *vice versa* (4T786-787). Dr. Rönnstrand did not cite this work in his report, even though he provided an opinion on this subject. In contrast, Dr. Van Etten stated that he was unaware of any such inhibitors as of 1993, and Dr. Heldin described this possibility as "theoretical" (8T1500-1501, 13T2658).

[304] From the evidence, I believe that the better view is that a skilled person would have known that the two proteins would likely have similar regulation, function and response to inhibitors.

(c) *Other Knowledge Relevant to the '203 Patent Compounds*

[305] As I noted above, the evidence before me dealt most extensively with the claim to imatinib (Claim 29) in the chemotherapy of CML (Claim 46). However, there was also considerable knowledge with respect to PDGF-R (for Group 2 compounds) and PKC (for Group 1 compounds). In addition, much was known about the potential for the role of PDGF-R in atherosclerosis. In very summary form, that evidence is set out as follows.

[306] It was a reasonable theory in 1993 that PDGF-R was implicated in atherosclerosis (Heldin Report, TX 71, paras 55, 58; 13T2605-2607, 2654-2657). Even Dr. Rönnstrand acknowledged that PDGF was found in atherosclerotic plaques and, at the time, was thought to play a role in atherosclerosis through the migration and proliferation of smooth muscle inside blood vessel walls (3T581, 591-592, 4T677-680).

[307] Drs. Van Etten, Heldin and Rönnstrand all agreed that the role of PDGF-R in cancer was a reasonable theory as of April 1, 1993.

[308] Links between PDGF-R and cancer known at this time and reviewed by Dr. Rönnstrand are as follows:

- The protein encoded by the viral oncogene, v-*SIS*, was known to be virtually identical to PDGF. Dr. Rönnstrand acknowledged that it was a reasonable hypothesis that uncontrolled cell growth in monkeys linked to v-*SIS* was caused by abnormal expression of PDGF or a related protein (3T544-545, 563-565, 575-578, 4T719-720).

- Dr. Rönnstrand agreed that there were human tumours known to be associated with PDGF in 1993. For example, there were elevated levels of PDGF expression in glioblastomas (3T556-558, 604-606, 4T718).

- Dr. Rönnstrand acknowledged that experiments had shown that PDGF antibodies may inhibit the growth of cancer cells. He stated that two reasonable theories to explain this result were that PDGF was causing the cancer and that the cells were not properly transformed (3T594-598).

[309] Therefore, Dr. Rönnstrand agreed with Dr. Heldin and Dr. Van Etten that a role for PDGF-R in cancer was a reasonable theory based on the state of the art in April 1993, even though there was no conclusive evidence at this time (Dr. Rönnstrand, 3T575-578; Van Etten Report, TX 37, paras 47-48, 144; 8T1493-1494; Heldin Report, TX 71, paras 47-49, 57, 196; 13T2597-2605).

[310] Some experimental results available in 1993 demonstrated that PKC might be implicated in cancer. However, this link is not as strong as it is for PDGF-R or ABL kinase (Heldin Report, TX 71, para 59; 14T2736, 2739-2740). These experimental results demonstrated a potential association between PKC and cancer by 1993:

- Tumour promoters applied to mouse skin in combination with a carcinogen were known to activate atypical and classical PKCs (Van Etten Report, TX 37, paras 45-46; 8T1485-1487).

- T24 bladder cancer cells contained an activated *H-RAS* gene, which researchers at the time believed was plausibly connected to the growth of these cells. Several PKC family members were known to play a role in RAS oncogene signalling (Van Etten Report, TX 37, para 151; 8T1487-1490).

[311] Dr. Heldin and Dr. Rönnstrand explained a theory that existed in 1993 concerning the role of PKC in multi-drug resistance. Dr. Heldin explained that cells exhibiting multi-drug resistance had increased expression of PKC and researchers at the time theorized that inhibiting PKC might decrease resistance (Heldin Report, TX 71, para 211; 13T2660-2662). Even Dr. Rönnstrand acknowledged that a skilled person in 1993 would have associated PKC and, therefore the Group 1 compounds only, with multi-drug resistance (4T723-726, 765-766).

(2) Summary of Line of Reasoning

[312] In sum, I am satisfied that there was an articulable line of reasoning connecting the desired result and the factual basis.

[313] Of particular relevance to this trial, as of April 1, 1993, the articulable line of reasoning for the use of the Group 2 compounds to treat CML was as follows:

1. any one of the Group 2 compounds had been demonstrated to selectively inhibit the v-ABL kinase;

2. it is a sound prediction that a compound that inhibits v-ABL will also inhibit BCR-ABL, due to the high degree of similarity between these two kinases;

3. there was "conclusive evidence" that CML was caused by the BCR-ABL kinase;

4. thus, it is a sound prediction, that imatinib (Claim 29) – or, indeed, any of the Group 2 compounds – would be useful in the treatment of CML.

[314] The relationship between v-ABL and BCR-ABL and between BCR-ABL and CML meant that the discovery of the selective inhibition attributes of the Group 2 compounds was the key to the treatment of CML. Even considering only the Ciba-Geigy *in vitro* testing, the strength of the knowledge about the kinases made the prediction of the utility of these compounds for the

"chemotherapy of tumours" overwhelming. The *in vivo* testing carried out by Ciba-Geigy was not essential to establish the line of reasoning; nevertheless, the fact that no experiments can be said to have "failed" strengthens the prediction and confirms the line of reasoning.

[315] With respect to the treatment of PDGF-R enabled tumours, the combination of the knowledge in the field and the testing carried out by Ciba-Geigy leads to a strong inference that these compounds would have utility in the treatment of PDGF-enabled tumours and in atherosclerosis.

[316] The link between PKC and the Group 1 compounds was much less certain. I do not believe that an articulable line of reasoning for the use of Group 1 compounds to treat atherosclerosis or for the chemotherapy of tumours has been established.

C. *Disclosure*

[317] The final requirement for a finding of sound prediction is that the basis for the sound prediction must be disclosed in the patent.

[318] The Plaintiffs complain that the sound prediction – if, indeed, one could be made – needed the disclosure of Ciba-Geigy's test data which were not included in the '203 Patent.

[319] In making this argument, the Plaintiffs rely heavily on the decision of my colleague, Justice Hughes, in *Eli Lilly Canada Inc v Apotex Inc*, 2008 FC 142, 63 CPR (4th) 406

[*Raloxifene (FC)*], aff'd 2009 FCA 97, 78 CPR (4th) 388 [*Raloxifene (FCA)*] to support their position that important data and test results should have been disclosed in the '203 Patent. I do not understand *Raloxifene (FC)*, or the subsequent affirmation of Justice Hughes by the Court of Appeal in *Raloxifene (FCA)*, to extend to the extreme position taken by the Plaintiffs.

[320] In *Raloxifene (FC)*, Justice Hughes concluded that the disclosure requirement for sound prediction had not been met. In that case, Eli Lilly had not disclosed, in the patent, the results of a study – referred to as the Hong Kong Study – which had been carried out by Eli Lilly prior to the Canadian filing date. The Hong Kong Study involved direct testing of raloxifene and, as found by Justice Hughes, was sufficient to turn the prediction that raloxifene would be effective in treating osteoporosis and bone loss into a sound prediction (*Raloxifene (FC)*, above at para 156). In other words, without the Hong Kong Study, Eli Lilly did not have a sound prediction that raloxifene would work as claimed.

[321] The singular importance of the Hong Kong Study was emphasized by the Court of Appeal, where it stated that (*Raloxifene (FCA)*, above at para 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. As the prediction was made sound by the Hong Kong study, this study had to be disclosed. [Emphasis added]

[322] In *Lovastatin (FC)*, I was faced with very similar arguments to those now before me. In that case, there was no question that some information known to the inventors was not disclosed in the patent. At paragraphs 527-528:

> I agree that the cross-examination of Mr. Alberts resulted in a list of facts and information that the inventors of the '380 Patent knew as of the Canadian filing date. One of the areas of interest relates to the dog studies carried out in 1979. Apotex pounces on this information as something that ought to have been disclosed in the '380 Patent in order to justify the sound prediction. However, I do not understand the jurisprudence to teach that the patent specification must disclose absolutely everything that that the inventor knew up to the relevant date. In [*Raloxifene (FC)*, above], without disclosure of the Hong Kong study, a skilled person would not have had sufficient information to understand the justification for the prediction. We must examine the specification to determine whether, with the information disclosed (even if there was more information available and undisclosed), a skilled person could have soundly predicted that the invention would work once reduced to practice.
>
> In the case of the '380 Patent, the question is whether sufficient information was disclosed to allow the skilled person to soundly predict that the compounds of the invention would be "useful as antihypercholesteremic agents for the treatment of atherosclerosis, hyperlipemia and like diseases in humans".

[323] The fact that all of the Ciba-Geigy tests are not described in the patent is not, in my view, fatal to Novartis's case. Applying the relevant jurisprudence to the '203 Patent now before me, the question is whether sufficient information was disclosed to allow the person of ordinary skill in the art to soundly predict that the compound of Claim 29 (imatinib) would be useful for the chemotherapy of tumours. I emphasize that the person to whom this question is relevant is a skilled person who would come to this exercise with the common general knowledge that is discussed above.

[324] A patentee cannot simply rely on the prior art to satisfy the requirements of disclosure; a patent must provide more disclosure than the prior art to satisfy the requirements of sound prediction (*Latanoprost*, above at para 44). Accordingly, I turn to the '203 Patent disclosure.

[325] In addition to the common general knowledge described above, the skilled reader of the '203 Patent would see that significant information with respect to both the Group 1 and 2 compounds is disclosed in the '203 Patent. The disclosure included both background information on the invention and information on and results of the more important tests carried out. In summary form, the following information is contained in the '203 Patent disclosure and is particularly relevant:

- Phosphorylation of proteins plays a significant role in cell differentiation and proliferation (page 5).

- Phosphorylation reactions are catalyzed by protein kinases, which may be divided into two groups: serine/threonine kinases and tyrosine kinases (page 5).

- PKC is an example of a serine/threonine kinase. PKC participates in many significant cellular processes, including cell proliferation and differentiation. Cellular functions in which PKC participates may be modified by modulating PKC enzyme activity (pages 5-6).

- Group 1 compounds are selective inhibitors of PKC. This provides Group 1 compounds with the potential to treat a number of conditions, including tumours and atherosclerosis (pages. 5-7, 24).

- The '203 Patent describes the testing of the Group 1 compounds. It cites a method to determine cell-free PKC inhibition using pig brain as well as method for conducting an anti-proliferation test using T24 bladder carcinoma cells. The patent provides IC_{50} ranges for each of these assays (pages 5-6).

- These test results demonstrate selective inhibition of PKC. Selectivity of inhibitors is important to reduce undesired side effects (page 6).

- PDGF-R is an example of a tyrosine kinase. PDGF is a growth factor that participates in both normal and pathological cell proliferation, which may be implicated in cancer and atherosclerosis (pages 5, 7).

- Group 2 compounds selectively inhibit PDGF-R and v-ABL tyrosine kinases and inhibit PKC virtually not at all. These inhibitory properties provide these compounds with the potential to treat tumours and non-malignant proliferative diseases, such as atherosclerosis (pages 7-8, 24).

- The '203 Patent also describes the testing of the Group 2 compounds. The patent cites methods for determining PDGF-R inhibition in cell-free test and a Western

> Blot test. It also describes a method for conducting an anti-proliferation test with respect to PDGF-R. For each of these three tests, an IC_{50} range is provided. The patent also cites a method to determine cell-free v-ABL inhibition, noting that this method was used to determine "[t]he above-mentioned inhibition" on page. 7, where an IC_{50} range is noted (pages 7-8).

[326] In my view, the disclosed information, together with the common general knowledge at that time, supports the sound prediction of the utility of Claim 46 when read together with Claim 29.

[327] With respect to the sound prediction of Claim 46, I am reminded of the patent considered by the Supreme Court in *AZT*, above. The Supreme Court noted, at paragraph 75, that the conclusions of the trial judge supported a finding of sound prediction; specifically:

> The trial judge has found that the inventors possessed and disclosed in the patent both the factual data on which to base a prediction, and a line of reasoning (chain terminator effect) to enable them to make a sound prediction at the time they applied for the patent.

I am faced with a very similar situation in this case.

[328] The '203 Patent discloses factual data related to selective inhibition of PDGF-R and ABL kinases by the Group 2 compounds. The patent also discloses explanations of how selective inhibition can lead to treatment of tumours. To this must be added the general information known in the relevant scientific community. Quite simply, that information – widely known and accepted – was to the effect that a compound that could selectively inhibit either PDGF-R or

v-ABL would have the potential for the treatment of tumours. As accepted by all of the experts, this link was well known to the point of being notorious.

[329] We are not speaking of speculation or remote possibility; rather, to repeat the words of Dr. Rönnstrand (4T642-643):

> I have nothing, no problem, with the idea that one should have pharmaceutical intervention with the growth factor signaling pathways in order to cure or treat cancer with kinase inhibitor or other inhibitors. I think that's a perfectly sound and valid idea at that time [April 1993] and today.

[330] The Plaintiffs argue that much needed to be done before one could conclude that any of the compounds could actually be used for treatment. They point to the lack of testing and argue that the Ciba-Geigy testing does not answer the following questions:

- Is the compound able to penetrate a cell, inhibit the relevant enzyme and show an anti-proliferative effect?

- Are the cultured cell lines reflective of a real disease state in an animal?

- Will the compound reach the site of action, and will it do so in sufficient quantity to achieve an antiproliferative effect *in vivo*?

- Will the compound retain its selectivity *in vivo* and thereby avoid toxic side effects?

[331] I agree with the Plaintiffs that further work would need to be done before any of the compounds – including imatinib – could be brought to market or could definitively be shown to treat cancer in warm-blooded animals. The problem with the Plaintiffs' position is that it goes beyond what is required for sound prediction. A further problem is that the Plaintiffs appear to require testing for each of the steps. Depending on the state of the knowledge in the scientific community, testing may not be required. For example, a reasonable inference concerning v-ABL and BCR-ABL could be drawn through the similarity of these two proteins, well known to the skilled person.

[332] Apotex and Novopharm (as it then was) made very similar arguments in *AZT*, above. For example, they argued that utility must be demonstrated by human clinical trials addressing regulatory requirements imposed by the Ministry of Health for drug submissions, such as toxicity, metabolic features, bioavailability and other factors (paras 24, 77). They also submitted that the invention was unpredictable at the filing date – mere "wishful thinking" – on the basis of the *in vitro* testing performed at that time (paras 55, 72). In *AZT* above, the Supreme Court responded to these arguments by stating, at paragraph 77:

> The prerequisites of proof for a manufacturer who wishes to market a new drug are directed to a different purpose than patent law. The former deals with safety and effectiveness. The latter looks at utility, but in the context of inventiveness. The doctrine of sound prediction, in its nature, presupposes that further work remains to be done. [Emphasis added.]

[333] While perhaps the Plaintiffs are not going as far in their arguments before me as they did in *AZT*, they are still demanding much more from the '203 Patent than is necessary to satisfy the doctrine of sound prediction. As explained above, I am satisfied that the testing that Ciba-Geigy

had carried out (and disclosed in the patent) coupled with the knowledge in the area leads to a sound prediction that imatinib would be useful as a chemotherapy treatment.

D. *Conclusion on Sound Prediction of the Use Claims*

[334] In summary on this question, I am not persuaded by the arguments of the Plaintiffs with respect to the use claims when read together with the Group 2 compound claims. There was a factual basis, a sound line of reasoning and disclosure of the prediction that any of the Group 2 compounds would be useful in the chemotherapy of ABL or PDGF-R tumours. Perhaps the strongest inference of all – because of the state of the art as of April 1, 1993 – was that a Group 2 compound would be useful in the treatment of "tumours", including CML.

[335] On the other hand, I find it difficult to conclude that the utility of the Group 1 compounds in either the chemotherapy of tumours or the treatment of atherosclerosis could have been soundly predicted as of April 1, 1993. While the Group 1 compound claims have demonstrated utility as selective inhibitors of PKC, the evidence of how this would translate to treatment of atherosclerosis or chemotherapy of tumours is not clear. This does not invalidate any of the use claims since these claims are to be read together with the individual compound claims.

X. Sufficiency or Adequacy of the Disclosure

A. *Introduction*

[336] As emphatically stated by the Supreme Court in the recent case of *Teva Canada Ltd v Pfizer Canada Inc*, 2012 SCC 60, 351 DLR (4th) 503 [*Sildenafil (SCC)*], at paragraph 34:

> Adequate disclosure in the specification is a precondition for the granting of a patent.

[337] Each of Teva and Apotex pleads – albeit in slightly different terms – that the specification of the '203 Patent is insufficient in that it does not provide adequate disclosure of the invention. Thus, in their view, the '203 Patent is invalid pursuant to s. 27 of the *Patent Act*.

[338] The requirement of disclosure is set out in s. 27(3) as follows:

27.	**27.**
. . .	. . .
(3) The specification of an invention must	(3) Le mémoire descriptif doit :
(*a*) correctly and fully describe the invention and its operation or use as contemplated by the inventor;	*a*) décrire d'une façon exacte et complète l'invention et son application ou exploitation, telles que les a conçues son inventeur;
(*b*) set out clearly the various steps in a process, or the method of constructing, making, compounding or using a machine, manufacture or composition of matter, in such full, clear, concise and exact	*b*) exposer clairement les diverses phases d'un procédé, ou le mode de construction, de confection, de composition ou d'utilisation d'une machine, d'un objet manufacturé ou d'un composé de matières,

terms as to enable any person skilled in the art or science to which it pertains, or with which it is most closely connected, to make, construct, compound or use it;	dans des termes complets, clairs, concis et exacts qui permettent à toute personne versée dans l'art ou la science dont relève l'invention, ou dans l'art ou la science qui s'en rapproche le plus, de confectionner, construire, composer ou utiliser l'invention;
(*c*) in the case of a machine, explain the principle of the machine and the best mode in which the inventor has contemplated the application of that principle; and	*c*) s'il s'agit d'une machine, en expliquer clairement le principe et la meilleure manière dont son inventeur en a conçu l'application;
(*d*) in the case of a process, explain the necessary sequence, if any, of the various steps, so as to distinguish the invention from other inventions.	*d*) s'il s'agit d'un procédé, expliquer la suite nécessaire, le cas échéant, des diverses phases du procédé, de façon à distinguer l'invention en cause d'autres inventions.

[339] Of further application, s. 27(4) of the *Patent Act* provides that:

(4) The specification must end with a claim or claims defining distinctly and in explicit terms the subject-matter of the invention for which an exclusive privilege or property is claimed.	(4) Le mémoire descriptif se termine par une ou plusieurs revendications définissant distinctement et en des termes explicites l'objet de l'invention dont le demandeur revendique la propriété ou le privilège exclusif.

B. *Teachings from Sildenafil (SCC)*

[340] The Supreme Court of Canada, in *Sildenafil (SCC)*, above, has provided comprehensive guidance on the importance and application of the disclosure requirement.

[341] In that case, the patent in issue (the '446 Patent) was a patent for the new use, the treatment of erectile dysfunction (ED), for an existing class of compounds, one of which was sildenafil. The '446 Patent contained seven claims, beginning with a claim to a huge class of compounds and ending with two specific compound claims, with Claim 7 relating to sildenafil. The evidence at trial established that, at the time of the patent application, Pfizer had conducted tests that demonstrated that sildenafil was effective in treating ED. None of the other compounds in the '446 Patent had been shown to be effective in doing so.

[342] The Supreme Court helpfully set out a framework for analyzing whether a patent satisfied the disclosure requirement. It was important to the Supreme Court to remind itself and us of the "bargain" or "quid pro quo" that is the basic policy rationale underlying the *Patent Act*. In paragraph 32, the court cited the words of Justice Binnie in *AZT*, above, at paragraph 37 where he stated, "Disclosure is the *quid pro quo* for valuable proprietary rights to exclusivity which are entirely the statutory creature of the *Patent Act*." Clarifying this general statement, the Supreme Court also noted the words of Lord Halsbury in *Tubes, Ltd v Perfecta Seamless Steel Tube Company, Ltd* (1902), 20 RPC 77 at pp. 95-96:

> [T]he object and the purpose of a specification is to enable, not anybody, but a reasonably well informed artisan dealing with a subject-matter with which he is familiar, to make the thing, so as to make it available for the public at the end of the protected period. [Emphasis added in *Sildenafil (SCC)*.]

[343] In determining that Pfizer had not complied with s. 27(3), the Court followed the reasoning from *Pioneer Hi-Bred Ltd v Canada (Commissioner of Patents)*, [1989] 1 SCR 1623, at 1638, 60 DLR (4th) 223. In that decision, the Court stated that: "[t]he description must be such as to enable a person skilled in the art or the field of the invention to produce it using only the

instructions contained in the disclosure". In *Sildenafil (SCC)*, the Supreme Court found that Pfizer had not complied with this requirement, as it was not clear which of the claimed compounds was effective for the treatment of erectile dysfunction. A skilled person would not have been able to determine which compound was effective without further testing. The lower Courts erred by limiting their consideration of the disclosure requirements to each of the individual compounds rather than to the specification as a whole.

[344] The analytical framework was set out by the Supreme Court in *Sildenafil (SCC)*, above at paragraph 70 and requires the court to answer three questions:

(a) What is your invention?

(b) How does it work?

(c) Having only the specification, can the person of ordinary skill in the art produce the invention using only the instructions contained in the disclosure?

[345] Applying this framework to the '446 Patent, the Supreme Court concluded that the disclosure requirement had not been met. Critical facts to this conclusion were as follows:

- The invention was the use of sildenafil for the treatment of ED.

- The specification did not indicate that sildenafil (Claim 7) was the effective compound.

- The public could not make "the same successful use of the invention as the inventor could at the time of his invention" because the reader would have to conduct "a minor research project" to determine which of Claims 6 or 7 was the "true invention" (para 74).

- Pfizer had the information needed to disclose the useful compound and "chose not to release it" (para 76).

- While the court did not take issue with the "cascading claims", the public's right to disclosure was denied "since the claims ended with two individually claimed compounds, thereby obscuring the true invention" (para 80).

C. *Nature of the Invention*

[346] As instructed by the Supreme Court of Canada in *Sildenafil (SCC)*, above at paragraph 53, the first step in determining whether the disclosure requirements of s. 27 have been met is to define the nature of the invention in the '203 Patent.

[347] Each of Novartis and the Plaintiffs agree that the '203 Patent discloses only one invention. They disagree on what that invention is.

- Novartis submits that the invention of the '203 Patent is a class of compounds that are novel selective kinase inhibitors. Nothing more.

- The Plaintiffs submit that the nature of the invention is that the formula I compounds will have a therapeutic effect *in vivo* against hyperproliferative disorders (tumours and atherosclerosis) and that, more specifically, the Group 2 compounds can be used to treat hyperproliferative disorders associated with the dysregulation of PDGF-R and ABL kinases. Nothing less.

[348] After careful reflection, and with great attention to the teachings of the Supreme Court in *Sildenafil (SCC)*, I agree, for the most part, with Novartis.

[349] The '203 Patent breaks down the claims into four categories; specifically, claims are to the compounds (Claims 1 to 39), pharmaceutical compositions comprising the compounds (Claims 40 to 43), the process to make the compounds (Claim 44) or the use of the compounds (Claims 45 to 48). The question is whether there is a "single general inventive concept" (*Sildenafil (SCC)*, above at para 64) which forms the foundation of the '203 Patent or whether this separation of the claims into categories results in four inventions. In this regard, it is not correct

to say, as the Plaintiffs argue, that there can be only one invention for any given patent. As pointed out by the Supreme Court in *Sildenafil (SCC)*, above at paragraph 64:

> It is possible, as in *Boehringer*, for each claim in a patent to disclose a separate invention. Where this issue is raised, however, individual patents must be considered on a case-by-case basis. In my view, the approach Teva advocates for at para. 119 of its factum is useful in this case: "... the specification as a whole must be examined to determine whether sildenafil and the other compounds claimed in the patent are linked so as to form a single general inventive concept". This is consistent with this Court's comment in *Consolboard*, at p. 520: "We must look to the whole of the disclosure and the claims to ascertain the nature of the invention and methods of its performance ... ." [Emphasis added.]

[350] However, in this case, I believe that there is a strong link among all of the claims which leads me to conclude that there is a single inventive concept. Alternatively, there are two inventions: one including the Group 1 compounds and the second including the Group 2 compounds.

[351] As argued by Novartis, the essence of the '203 Patent is the invention of a class of compounds. The nature of the invention is reflected throughout the specification, beginning with the title of the '203 Patent “Pyrimidine Derivatives and Processes for the Preparation Thereof”. This is the first and most important invention of the '203 Patent. The '203 Patent is a complex patent, including many compounds and four types of claims. However, whether the claims are to the compounds (Claims 1 to 39), pharmaceutical compositions comprising the compounds (Claims 40 to 43), the process to make the compounds (Claim 44) or the use of the compounds (Claims 45 to 48), the essential link is the invention of a class of compounds, each one of which can selectively inhibit certain kinases.

[352] The problem with the Plaintiffs' description of the nature of the invention is that it treats the '203 Patent as a use patent only and ignores the fact that the '203 Patent is, above all, a patent to one or, possibly two, classes of novel compounds. On this basis, the Plaintiffs leap immediately to the utility of the compounds. Utility is a different concept that is considered earlier in these reasons. Although some of the claims are for the use of the compounds, the overall inventive concept of the patent was the finding by Dr. Zimmermann and the team of scientists at Ciba-Geigy that certain compounds, as claimed, could selectively inhibit kinases as follows:

1. The Group 1 compounds selectively inhibit PKC; and

2. The Group 2 compounds selectively inhibit either PDGF-R or ABL.

[353] This assessment is reflected in the words of the '203 Patent where the link between the compounds and potential therapeutic treatment is directly stated in phrases such as:

- Owing to their inhibiting activity towards protein kinase C, the compounds of formula I, where R_4 and R_8 are hydrogen, . . .can be used . . . (second full paragraph, page 6);

- Owing to the properties described, the compounds of formula I, where R_4 and R_8 are hydrogen, . . . can be used . . . (second full paragraph at page 7);

- Owing to the properties described, compounds of formula I can be used not only as tumour-inhibiting active ingredients . . . (third full paragraph, page 8).

[354] It is not because of some use of a compound, which use was discovered and claimed subsequent to the discovery and patenting of the compounds (as was the case in *Sildenafil (SCC)* and *AZT*), that the compounds have potential use. Rather, the potential uses are inherent in the properties of the novel compounds invented in the Ciba-Geigy laboratories.

[355] I also believe that it may be more in keeping with the nature of the invention disclosed by the '203 Patent to treat the '203 Patent as being two inventions: one for each of Group 1 and Group 2. Unlike *Sildenafil (SCC)*, in which there was nothing to distinguish sildenafil from any of the other claimed compounds (para 66), there is an undisputed evidentiary basis for the two inventions of the '203 Patent. As acknowledged by every one of the experts, the two groups of compounds are readily identifiable by a person of ordinary skill in the art. Throughout the disclosure and the claims themselves, there is a clear delineation of the two groups of compounds. Not only can the compounds be identified by their organic structure, the potential use of each group is clearly set out. This does not mean that I should consider each claim as a separate invention; rather, groups of claims could be considered together.

D. *Practising the Invention*

[356] The Plaintiffs make no submissions on the second question of the sufficiency analysis. I assume that the patent meets the obligation of explaining how the invention works.

[357] Thus, the final question to be addressed is this:

> Having only the specification, can the person of ordinary skill in the art produce the invention using only the instructions contained in the disclosure?

[358] Because the parties have focussed on the Group 2 claims, I will consider this question in light of the Group 2 compounds. The specific compounds that fall within Group 2 are described in the Examples and claimed in Claims 28 to 33. These are the compounds that selectively inhibit either PDGF-R or ABL.

[359] I begin by considering what the person of ordinary skill in the art would be able to do with the '203 Patent and nothing else before him or her. In addition to the specification, the hypothetical skilled person would approach the patent with the knowledge of the state of the art, as discussed above. As a result of the disclosure and the prior art, the skilled reader would be able to:

- Identify which claimed compounds belong to Group 2;
- Make any of the Group 2 compounds;
- Determine the level of inhibition of v-ABL by using the methods set out in the disclosure (page 8, second full paragraph);
- Determine the level of inhibition of PDGF-R by using the methods set out in the disclosure (p. 8, first full paragraph);

- Understand that the compounds, because of their properties, could be used "as tumour-inhibiting active ingredients" and as drugs against "other non-malignant anti-proliferative diseases" (such as atherosclerosis) (page 8, third paragraph).

[360] Not a single Group 2 compound was included in the '203 Patent for which there was no positive data. In other words, all six individually claimed Group 2 compounds were tested in the Ciba-Geigy laboratories and all six exhibited selective inhibition of the v-ABL and PDGF-R enzymes. That information was not hidden from the public.

[361] Contrast the disclosure of the '203 Patent to the '446 Patent in *Sildenafil (SCC)*. There, the patent did not expressly disclose that sildenafil was the only compound (of the two compounds specifically claimed) that had been tested and found to work. This omission led the trial judge to comment that the sildenafil patent disclosure "plays games with the reader" (*Pfizer Canada Inc v Novopharm*, 2009 FC 638 at para 135, 76 CPR (4th) 83 [*Sildenafil II FC*]) and, ultimately, to the conclusion of the Supreme Court that there had been inadequate disclosure.

[362] The Plaintiffs raise a number of omissions from the '203 Patent disclosure that, in their opinion, prevent the skilled person from putting the invention into practice. The first problem with all of their submissions on this point is that they have elevated the "invention" beyond reason. As I have observed above, this is not a use patent; it is a patent which claims novel compounds that were unarguably invented by Dr. Zimmermann and the Ciba-Geigy team.

[363] It is important to remember that, as of April 1, 1993, imatinib was far from the point where it could be used as a drug to treat CML. By that date, Ciba-Geigy scientists had identified a number of Group 2 compounds that were selective inhibitors of ABL but had not carried out the follow-up testing to determine which one of those six compounds would proceed for further drug development or to clinical trials. Faced with the information contained in the disclosure, a person of ordinary skill in the art would be in no worse position than the Ciba-Geigy scientists. The skilled person would know, from the disclosure alone, that six compounds selectively inhibited ABL and had the potential to treat CML. Moreover, just as Ciba-Geigy had to do after the filing date, the "reasonably well informed artisan" could carry out the post-filing date experimentation and testing that would take any one of those molecules from its inventive concept (selective inhibition) to the predicted treatment.

[364] The state of Ciba-Geigy knowledge about the Group 2 compounds is borne out through the testimony of Drs. Zimmermann, Lydon and Fabbro and through a number of documents.

[365] The argument advanced by the Plaintiffs that the patent should have specified which inhibitors were the best does not address the totality of the evidence, which suggests that the PK Group itself did not have this information at the time of filing. These researchers had found a number of effective inhibitors and had yet to perform further testing to determine which inhibitor would be most appropriate for drug development.

[366] This was demonstrated during the trial in two ways. Firstly, this conclusion is supported by the Ciba-Geigy cell-free test results, analyzed and accepted by the experts without dispute, as

noted above. These test results demonstrated that all six individually claimed Group 2 compounds were effective inhibitors of v-ABL kinase. Secondly, this is shown through the testimony of Dr. Zimmermann and Dr. Lydon as well as contemporaneous reports and other documentation. I will review this evidence briefly.

[367] There was no attempt to hide the best inhibitor or inhibitors, since the PK Group at Ciba-Geigy was still evaluating inhibitor candidates for drug development. As of April 1, 1993, CGP 53716 was the compound of highest priority (Dr. Zimmermann, 12T2361; CGP 53716 Biology Report, TX 55, Tab 2; Druker Contract, TX 63). However, according to Dr. Lydon and Dr. Zimmermann, CGP 53716 presented its own challenges relating to solubility and the researchers had developed a number of other compounds that were highly selective (Dr. Lydon, 10T2020-2021, 2109, 2113; Dr. Zimmermann, 12T2316-2318, 2361, 2391-2395). At this time, CGP 57148 "had a good start" in the Ciba-Geigy laboratories, but much work remained to be done (Dr. Zimmermann, 12T2309-2310; Dr. Lydon, 10T1976-1980). Further, after the patent was filed, CGP 53716, 57148 and 57012 – all individually claimed Group 2 compounds – were sent to Dr. Druker for use in his experiments (TX 63). Although CGP 53716 was noted as the compound of highest priority, all of these compounds were presented as "relatively selective v-*abl* tyrosine protein kinase inhibitors with *in vitro* IC50 values between 0.04 – 1.5 μM" (Druker Contract, TX 63). It was not until Dr. Druker's "pivotal" experiments were completed that the researchers presented the Ciba-Geigy work and Dr. Druker's work in support of the development of imatinib in particular as a drug against CML (Lydon testimony, 11T2163-2164).

[368] Focussing on the selective inhibition of v-ABL kinase by the six specifically claimed Group 2 compounds, the failure of the inventor to disclose more information about the testing of those compounds is troubling. Is the omission of information from the disclosure fatal to the '203 Patent? The Plaintiffs assert that it is; I do not agree.

[369] The Plaintiffs raise four main concerns with respect to the absence of information in the '203 Patent. I will attempt to summarize each argument and then deal with it.

> Argument 1: The skilled reader is left to believe that all of the Group 2 compounds inhibit PDGF-R and ABL kinase equally, since broad IC_{50} ranges are provided for PDGF-R kinase and no ABL kinase data is provided.

[370] The first of these arguments is, in effect, an argument that the specific data are not disclosed with respect to the ABL inhibition. Of specific concern to the Plaintiffs, the specification does not disclose that Ciba-Geigy obtained an IC_{50} value of 0.038µM for the compound CGP 57148 against v-ABL kinase. In the opinion of the Plaintiffs, had the skilled person known that the IC_{50} value for compound CGP 57148 was 0.038µM, he or she would have immediately known – as the inventor did – that this compound was vastly superior to the other Group 2 compounds. Thus, the Plaintiffs submit that the omission of that critical data point obscured the invention and would have required the skilled person to conduct testing on all six compounds to discover which of the six would perform to the same level as was known by the inventors.

[371] There are three reasons why this argument is not persuasive.

[372] The first response is, as discussed above in the section of these reasons on the proper construction of the patent, the IC_{50} values included in the first full paragraph at p. 8 of the '203 Patent apply to the ABL kinase inhibition as well as to the inhibition of PDGF-R. By including the words "The above-mentioned inhibition of v-abl-tyrosine kinase" in the second full paragraph, the reader is directed to the IC_{50} values on page 7 of the '203 Patent. Even if I am wrong in this finding, two further reasons lead me to reject the Plaintiffs' argument on this point.

[373] The second answer to this argument is that, in general, an absence of data does not go to the question of s. 27(3) sufficiency. Novartis relies on the Federal Court of Appeal decision in *Pfizer Canada Inc v Canada (Minister of Health),* 2008 FCA 108, 67 CPR (4th) 23 [*Atorvastatin (FCA*)] to argue that missing data does not go to s. 27(3) sufficiency. As stated in that case, at paragraph 56:

> The Applications Judge was wrong in interpreting the disclosure requirement of subsection 27(3) of the Act as requiring that a patentee back up his invention by data**.** By so doing, he confused the requirements that an invention be new, useful and non-obvious with the requirement under subsection 27(3) that the specification disclose the "use" to which the inventor conceived the invention could be put: see *Consolboard, supra*, at 527. Whether or not a patentee has obtained enough data to substantiate its invention is, in my view, an irrelevant consideration with respect to the application of subsection 27(3). An analysis thereunder is concerned with the sufficiency of the disclosure, not the sufficiency of the data underlying the invention. Allowing Ranbaxy to attack the utility, novelty and/or obviousness of the 546 patent through the disclosure requirement unduly broadens the scope of an inventor's obligation under subsection 27(3) and disregards the purpose of this provision.

[374] As I understand the facts of that case, the data in question was not required for the notional skilled person to "use" or work the invention. The Court of Appeal, observed that the

promise of the patent in issue was that "the compounds covered have an 'unexpected and surprising inhibition of biosynthesis of cholesterol'" (para 54). The inventor was not making any claim to the level of inhibition and, therefore, the data was unnecessary for the disclosure requirement of s. 27(3). Even without the data, the skilled person could make the compounds in question, thereby "using" the invention.

[375] In my view, the teaching of *Atorvastatin (FCA)* is that a lack of data cannot in and of itself result in a finding of insufficiency. Rather, one must ask whether the omission of the data from the patent prevents the person of ordinary skill in the art from using the invention as contemplated by the inventor. In the case before me, the lack of data does not prevent the skilled person from using the invention as contemplated. The experts who reviewed the testing carried out by Ciba-Geigy confirmed that all six Group 2 compounds revealed impressive IC_{50} values when tested, thereby indicating that any one of those compounds could have the potential for further development into useful drugs. The inclusion of specific data points or IC_{50} values would not have added to the specification statement or promise in the '203 Patent that all of the Group 2 compounds would selectively inhibit v-ABL (or PDGF-R).

[376] The final reason for rejecting this data argument is that the Plaintiffs are really raising a "best mode" argument. In other words, the Plaintiffs are asserting that the '203 Patent should have disclosed that CGP 57148 was the best of the six compounds. In the face of the evidence that all six compounds were effective inhibitors, this argument cannot be sustained.
Section 27(3)(c) of the *Patent Act* requires that an inventor must " in the case of a machine, explain the principle of the machine and the best mode in which the inventor has contemplated

the application of that principle" (emphasis added). There is no requirement in s. 27(3) that "best mode" must be disclosed in inventions that are not machines.

> Argument 2: Dr. Van Etten testified that Group 2 compounds would inhibit either PDGF-R kinase related tumours or ABL kinase related tumours. However, there is no indication in the patent which Group 2 compounds are useful against which tumours.

[377] I agree that the patent does not distinguish which of the individually claimed Group 2 examples may be effective against tumours. A fair characterization of Dr. Van Etten's evidence is that at least one of the individually claimed compounds could be used for the chemotherapy of tumours mediated by PDGF-R kinase or ABL kinase. However, Dr. Van Etten could not tell from reading the patent alone which compound or compounds are effective against tumours, let alone which compounds have activity against which tumours (TX 37, para 150; 8T1600-1608). The Plaintiffs argue that the inventor knew that imatinib had striking potency against ABL kinase, while other Group 2 compounds were more potent against PDGF-R kinase compared to ABL kinase. Further, the inventor also had *in vivo* data indicating a positive effect against PDGF-R driven tumours by four Group 2 compounds. According to the Plaintiffs, none of this information was disclosed.

[378] In my view, these failures of disclosure do not offend s. 27(3) of the *Patent Act*. All that is required by *Sildenafil (SCC)*, above at paragraph 70, is that the reader of the patent can discern what the invention is, how it works and how to make same successful use of the invention as the inventor could at the time he filed the patent. The omissions that the Plaintiffs complain of relate to distinctions that do not form part of the true invention. These alleged omissions reflect work

that, for the most part, had yet to be done. Further, these arguments amount to complaints relating to the disclosure of data, which is not legally required. On this basis, the Plaintiffs' assertions in this regard are fundamentally flawed.

[379] Taking into account this context and the description of the invention by the inventor, the Plaintiffs set the bar too high. The Plaintiffs rely solely on the testimony of Dr. Van Etten, and cannot point to a single reference in the patent itself which suggests that the distinction they raise is relevant to that which the inventor truly invented. Section 27(3) is not meant to invalidate patents on the basis of distinctions which do not underlie the true invention. In focussing too heavily on the therapeutic use component of the '203 Patent, the Plaintiffs fail to appreciate the nature of the invention as a whole, as articulated by the Supreme Court in *Sildenafil (SCC)*, above at paragraphs 58-68.

[380] Further, a review of the Novartis test results demonstrates that Ciba-Geigy would not have been in a position to conclusively differentiate between the Group 2 compounds on the basis of which type of tumours they inhibit. Firstly, as Dr. Lydon explained, Ciba-Geigy was uncertain whether their v-ABL cell line was truly v-ABL dependent (Dr. Lydon, 10T2070, 2095). As well, Ciba-Geigy had only performed one *in vivo* v-ABL dependent tumour experiment, which was inconclusive because of a solubility problem concerning CGP 53716 (see for example, Dr. Rönnstrand's testimony, 4T842-843). On this basis, it would have been impossible for the inventors to draw specific conclusions relating to the relative ability of Group 2 compounds to inhibit v-ABL and PDGF-R mediated tumours. Therefore, this distinction

cannot be necessary for the skilled reader to use the invention in the same successful way as the inventor.

> Argument 3: The skilled reader is left with no awareness of the solubility problem encountered in relation to CGP 53716.

[381] Although CGP 53716 looked promising before the patent was filed, the Ciba-Geigy scientists realized that the rate of dissolution of this compound was low (Dr. Zimmermann, 12T2295-2296). An awareness of this problem began when the PK Group began testing this compound (Dr. Zimmermann, 12T2316-2317; Dr. Lydon, 11T2255). The Plaintiffs argue that the seriousness of this problem would have prevented CGP 53716 from ever becoming an effective compound and this should have been disclosed.

[382] The first problem with this argument is that, in spite of its solubility issue, CGP 53716 was still considered by the Ciba-Geigy scientists to be a very promising compound. CGP 53716 remained the lead compound in April 1993 and for a number of months afterwards. Even as late as September 1993, when Ciba-Geigy approached Dr. Druker to carry out further tests, CGP 53716 was still a compound of great interest.

[383] The second reason why this argument is not persuasive is that the solubility problem could be solved through relatively simple means. Indeed, that is what was done at Ciba-Geigy. Dr. Lydon explained that CGP 53716 was combined with number of solvents such as tween, DMSO and ethanol, in hopes of improving solubility in an animal model (Dr. Lydon,

10T2020-2021). In particular, for the *v-SIS* xenograft mouse tumour experiments, tween 80, a surfactant, was used to improve the bioavailability of CGP 53716 (Dr. Lydon, 10T2090).

[384] In sum, all that is necessary, for the skilled person to use CGP 53716 successfully, is a proper solvent system including a surfactant such as tween (11T2229-2230). Although the Supreme Court stated that a skilled reader should not have to engage in a minor research project (*Sildenafil (SCC)*, above, at para 75), this does leave open the possibility that some trial and error may be permitted. The identification of a solubility problem and the application of what is a routine modification in the testing protocol is, in my view, a matter of simple trial and error on the part of the person of ordinary skill in the art – and not, as argued by the Plaintiffs, a "research project". This means that lack of disclosure of the minor problem of poor solubility of CGP 53716 and the solution adopted by the PK Group at Ciba-Geigy were not critical to the understanding or practice of the invention.

> Argument #4: No *in vivo* results are disclosed, even though the PK Group tested compounds *in vivo*.

[385] The failure to refer to the *in vivo* test results does not constitute a fatal flaw in the '203 Patent. This is because the invention does not require the disclosure of *in vivo* data to permit the person of ordinary skill in the art to put the invention into practice.

[386] Adapting the words of the Supreme Court in *Sildenafil (SCC)*, I conclude that, having only the specification of the '203 Patent, the person of ordinary skill in the art could produce the

invention using only the instructions contained in the disclosure. The third part of the adequacy analysis is satisfied.

E. *Conclusion on Sufficiency*

[387] In conclusion on this issue, I am not persuaded that the '203 Patent fails to meet the disclosure requirement of s. 27(3) of the *Patent Act*. In *Sildenafil (SCC)*, above at paragraph 80, the Supreme Court identified the "key issue" with respect to s. 27(3) disclosure as follows:

> As a matter of policy and sound statutory interpretation, patentees cannot be allowed to "game" the system in this way. This, in my view, is the key issue in this appeal. It must be resolved against Pfizer.

In the case before me, I am satisfied that the patentee did not "game" the system.

XI. Apotex Infringement

[388] One issue that is unique to Apotex is the question of infringement. Apotex has acknowledged that it has in its possession certain volumes of bulk imatinib and has used this material in a number of ways, as discussed below. Novartis does not seek damages with respect to this allegedly infringing material; however, it does ask for the following:

1. a declaration that Apotex has infringed: Claims 5, 7 and 29; Claim 46, as read with Claims 5, 7 or 29; and Claim 44; and

2. an injunction and delivery up of any infringing material, consisting of all material made to date that is not explicitly required to be maintained for regulatory purposes.

[389] In response, Apotex asserts that all of the imatinib material: has been or will be used for regulatory or experimental use; and has not been and will not be used for commercial purposes. As such, it is exempt from infringement under s. 55.2(1) and (6) of the *Patent Act* and at common law.

[390] For the reasons that have been set out above, I have concluded that Claims 5, 7 and 29; Claim 46, as read with Claim 29; and Claim 44 are valid. Imatinib falls within all of those claims. Apotex acquired and has used – or holds in inventory – a total of **[Redacted]** kg of imatinib. It follows that, but for the regulatory and experimental use exemptions, Apotex would have infringed the specified claims of the '203 Patent. The issue is whether any or all of these volumes qualify for the statutory exemption under s. 55.2 of the *Patent Act*.

[391] I begin with the proposed exemption from infringement based on s. 55.2(1) and (6) of the *Patent Act*. That provision states that:

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	**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,

that regulates the manufacture, construction, use or sale of any product.	provinciale ou étrangère réglementant la fabrication, la construction, l'utilisation ou la vente d'un produit.
. . .	. . .
(6) For greater certainty, subsection (1) does not affect any exception to the exclusive property or privilege granted by a patent that exists at law in respect of acts done privately and on a non-commercial scale or for a non-commercial purpose or in respect of any use, manufacture, construction or sale of the patented invention solely for the purpose of experiments that relate to the subject-matter of the patent.	(6) Le paragraphe (1) n'a pas pour effet de porter atteinte au régime légal des exceptions au droit de propriété ou au privilège exclusif que confère un brevet en ce qui touche soit l'usage privé et sur une échelle ou dans un but non commercial, soit l'utilisation, la fabrication, la construction ou la vente d'une invention brevetée dans un but d'expérimentation.

[392] It is settled law (and Novartis does not dispute) that Apotex may claim an exemption from liability for certain amounts of the infringing product (*Merck & Co v Apotex Inc*, 2006 FC 524 at para 153, 53 CPR (4th) 1 [*Merck (FC)*], rev'd on other grounds 2006 FCA 323, [2007] 3 FCR 588 [*Merck (FCA)*], leave to appeal to SCC refused, [2006] SCCA No 507; *Perindopril*, above at para 163; *Cefaclor*, above at para 344). However, in order to claim an exemption under either s. 55.2 of the *Patent Act* or at common law, Apotex bears the burden of demonstrating that the imatinib inventory was used for experimental or regulatory uses and that no portion of the inventory was or will be used commercially.

[393] Through Mr. Fahner, in particular, and other fact witnesses, Apotex led substantial and carefully prepared evidence of the volumes of imatinib API product that it (or its affiliate Apotex Pharmachem Inc.) had obtained and the uses to which the material had been put.

[394] Specifically, Apotex lists a number of its uses of bulk imatinib, asserting that these uses do not constitute infringement (Apotex's Further Further Amended Reply and Defence to Counterclaim at para 41B). These activities include:

1) Use of imatinib for research and development purposes, such as determination of whether bulk imatinib is suitable, formulation development, pre-clinical and clinical studies and bioequivalence testing;

2) Use of imatinib for internal and external quality control purposes;

3) Use of imatinib to comply with federal regulatory requirements under the Canadian *Food and Drug Regulations*, CRC c-870;

4) Use of imatinib to comply with the provincial regulatory requirements under the *Drug Interchangeability and Dispensing Fee Act*, RRO 1990, Reg 935, s 6;

5) Use of imatinib to comply with the United States *Federal Food, Drug and Cosmetic Act*, 21 USC § 301 and the regulations prescribed under the Act; and,

6) Use of imatinib to comply with other foreign regulatory requirements.

[395] Based on the evidence of Mr. Fahner, I am satisfied that all but **[Redacted]** kg of bulk API was obtained and has been used for the purposes of: (a) developing suitable formulations

and processes; (b) obtaining regulatory approval to sell commercial formulations; and (c) demonstrating that its manufacturing process could be carried out on a commercial scale. As such, Apotex is exempt from a finding of infringement of the specified claims of the '203 Patent with respect to those volumes of bulk imatinib which have been used.

[396] The only potential problem arises with respect to approximately **[Redacted]** kg (the Inventory Bulk Imatinib) that remains in Apotex's inventory. **[Redacted]** Novartis submits that this Inventory Bulk Imatinib should be delivered up. There are three reasons why I am not inclined to grant Novartis's request.

[397] Firstly, the uncontested testimony of Dr. Sherman, Mr. Fahner and Ms. Ayyoubi is that all of the Inventory Bulk Imatinib exceeds the manufacturer's expiry date and, absent retesting by the vendor, could not be used for commercial purposes. As explained by Ms. Ayyoubi (6T1285):

> If the lot of API is not used before the expiry date, for commercial manufacturing it needs to be retested to ensure that it complies to the specification.
>
> For formulations and developmental work it can be used to conduct some experiments, but for commercial manufacturing it must be within the expiry date for both the vendor expiry date and [Apotex's] internal expiry date, in order for this to be released for commercial manufacturing.

[398] Secondly, even if the material is not retested, Apotex may be able to use the remaining lots of bulk imatinib for "further experimental and processing evaluation" within the research and development laboratory or has the option of "sending them back to the vendor for a

processing or a credit" (Mr. Fahner, 6T1330-1331). In either case, the result would be that the Inventory Bulk Imatinib would not find its way into the commercial stream.

[399] Finally, we have the undertaking of Dr. Sherman, made during his testimony, that the Inventory Bulk Imatinib will never be used commercially (2BT103).

> [Y]ou've got my undertaking that we will not be selling commercially any of the material that is in our possession. It was -- or that we will acquire before patent expiry, before the patent is held invalid.
>
> There are particular circumstances in this case where we have concern that the patent could be held valid, and we hope it won't be obviously, but in this case [that the 203 Patent is held to be valid] I have given a commitment to you, and I will honour it, that we will not be using commercially any of the material that we have brought in for development purposes. That's what it will be used for, and the balance of it if it's not used when it expires will be thrown out. [Emphasis added.]

[400] On the basis of the evidence before me and the undertaking of Dr. Sherman, I will not order the delivery up of the Inventory Bulk Imatinib. However, the judgment will incorporate the undertaking of Dr. Sherman.

[401] In sum, I am satisfied that:

1. all of the imatinib acquired by Apotex (or its affiliate), but for the Inventory Bulk Imatinib, is exempt from infringement under s. 55.2(1) and (6) of the *Patent Act* and at common law; and

2. Apotex will not be ordered to deliver up the Inventory Bulk Imatinib, subject to the undertaking of Dr. Sherman and order of this Court that it will not be used commercially and will be destroyed after reaching its expiry date.

XII. Conclusion

[402] In conclusion, for the most part, the claims of Teva and Apotex will be dismissed. The Plaintiffs have failed to persuade me that Claims 5, 7 and 9 to 48 of the '203 Patent are invalid, void and of no force and effect.

[403] On the other hand, the Plaintiffs have met their burden with respect to Claims 1, 2, 3 and 4. Specifically, these claims will be held to be invalid, void and of no force and effect on the basis that Novartis could not soundly predict that all of the compounds included in those claims could be predicted to have utility as selective inhibitors of PKC, PDGF-R or ABL kinases.

[404] I note that Apotex and Teva, in their respective Statements of Claim, sought declarations that Claims 40 to 43 are invalid. No submissions were made in final argument with respect to these claims. I assume that the Plaintiffs no longer seek a declaration that these claims are invalid.

[405] In its counterclaims to these actions, Novartis seeks a declaration that Claims 1 to 5, 7, 29 and 40 to 48 of the '203 Patent are valid. In final argument, however, Novartis focussed only on: Claims 5, 7, 29; Claims 45 and 46 when read with any of these compound claims; and Claim 44.

In final argument, Novartis referred to Claim 45. Claim 45 is a claim to the use of the compounds in the treatment of atherosclerosis. Novartis did not refer to this claim in its opening statement. In addition, evidence led during the trial addressed this use only peripherally. While I am not prepared to invalidate Claim 45, I am also not persuaded that I have a sufficient evidentiary base to declare it to be valid. Therefore, I find that, as between the parties, Claims 5, 7, 29, Claim 46 (when read with any of these compound claims) and Claim 44 are valid.

[406] For the reasons above, I have concluded that Novartis's claim for an injunction and delivery up of Apotex's remaining bulk imatinib is not warranted. However, the undertaking of Dr. Sherman in respect of the Inventory Bulk Imatinib will be incorporated into the Judgment.

[407] As the successful party, Novartis is entitled to its costs. As requested by Novartis (and not commented on by the Plaintiffs), its costs should include post-judgment interest from the date of the judgment to the date of payment at a rate of 5% pursuant to s. 4 of the *Interest Act*, RSC c I-15. Beyond this, I hope that the parties can agree on the issue of costs. However, in the event that the parties cannot agree on costs, they may serve and file submissions, not to exceed ten pages in length, within 60 days of the date of Judgment. The parties will have a further 15 days to serve and file a reply, not to exceed five pages in length.

[408] Finally, I thank the parties for their co-operation, courtesy and professionalism throughout the trial.

POSTCRIPT

[1] The Confidential Reasons for Judgment were released to the parties on February 8, 2013. Upon release of the Confidential Reasons, the parties were requested to advise the Court of portions of the Reasons for Judgment that they wished redacted for the Public Reasons. On February 14, 2013 and February 15, 2013, in separate letters, counsel for Novartis AG and Novartis Pharmaceuticals Canada Inc. and counsel for Teva Canada Limited advised the Court that there were no portions of the Reasons for Judgment that should be redacted. Counsel for Apotex Inc. made submissions by letter to the Court dated February 15, 2013 requesting certain redactions be made.

[2] These Reasons for Judgment contain redactions made to the Confidential Reasons for Judgment that were issued on February 8, 2013, pursuant to the Amended Protective Order dated December 13, 2011. The redactions were made in accordance with the correspondence received from the solicitors for Apotex Inc., with which this Court agrees, and are now incorporated in the within Public Reasons for Judgment.

"Judith A. Snider"

Judge

Ottawa, Ontario
Public Reasons – February 19, 2013
Confidential Reasons February 8, 2013

FEDERAL COURT

SOLICITORS OF RECORD

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APPEARANCES:

Andrew Brodkin Daniel Cappe Dino Clarizio David Scrimger Nando DeLuca Michel Anderson	FOR THE PLAINTIFF APOTEX INC. (T-833-11)
Jonathan Stainsby Andrew McIntyre Andrew Skodyn Lesley Caswell	FOR THE PLAINTIFF TEVA CANADA LTD. (T-2021-10)
Anthony Creber Isabel Raasch John Norman Jennifer Wilkie Marc Richard	FOR THE DEFENDANT (T-833-11 and T-2021-10)

SOLICITORS OF RECORD:

Goodmans LLP Barristers and Solicitors Toronto, Ontario	FOR THE PLAINTIFF APOTEX INC. (T-833-11)
Heenan Blaikie LLP Barristers and Solicitors Toronto, Ontario	FOR THE PLAINTIFF TEVA CANADA LTD. (T-2021-10)
Gowling Lafleur Henderson LLP Barristers and Solicitors Ottawa, Ontario	FOR THE DEFENDANT (T-833-11 and T-2021-10)