Federal Court  Cour fédérale

Date: 20170321

Docket: T-1100-15

Citation: 2017 FC 296

Ottawa, Ontario, March 21, 2017

PRESENT: The Honourable Mr. Justice Manson

BETWEEN:

BRISTOL-MYERS SQUIBB CANADA and BRISTOL-MYERS SQUIBB HOLDING IRELAND

Applicants

and

APOTEX INC. AND THE MINISTER OF HEALTH

Respondents

JUDGMENT AND REASONS

I. Introduction and Issues

[1] The Applicants in this action are Bristol-Myers Squibb Canada ("BMS-Canada") and Bristol-Myers Squibb Holdings Ireland ("BMS-Ireland") (collectively, the "Applicants"). BMS-Canada is a Canadian pharmaceutical manufacturer that distributes and sells, among other things, the pharmaceutical SPRYCEL®. BMS-Canada is a first person as defined in the *Patented Medicines (Notice of Compliance) Regulations*, SOR/93-133, subsections 2(1) and 4(1) (*PM(NOC) Regulations).* BMS-Ireland is the owner of Canadian Patent Nos. 2,366,932 (the "'932 Patent") and 2,519,898 (the "'898 Patent").

[2] For purposes of this application, both the ‘932 and the ‘898 Patents (together the “BMS Patents”) generally relate to the compound dasatinib, and have been listed on the Patent Register with respect to SPRYCEL®, pursuant to section 4 of the *PM(NOC) Regulations*.

[3] The Respondent, Apotex Inc. (the “Respondent”), is a generic pharmaceutical manufacturer. It filed an Abbreviated New Drug Submission (“ANDS”) with the Minister of Health (the “Minister”) seeking a Notice of Compliance (“NOC”) for APO-Dasatinib, using SPRYCEL® as the Canadian reference product. It served Notices of Allegation (“NOA”) regarding the ‘932 Patent and the ‘898 Patent (the ‘932 NOA and the ‘898 NOA, respectively), on May 26, 2015.

[4] The Applicants commenced this prohibition application on July 2, 2015, seeking orders that the Minister be prohibited from issuing a NOC to Apotex for APO-Dasatinib until after the ‘932 and the‘898 Patents expire.

A. *Issues*

[5] The issues are characterized in the ‘932 NOA and the ‘898 NOA as follows:

The ‘932 Patent:

1. Are the claims 1 to 6 and 8 to 43 irrelevant for failing to contain a claim for the medicinal ingredient, the formulation, the dosage form, or an approved use of the medicinal agreement?
2. Does APO-Dasatinib infringe the ‘932 Patent?
3. Is the ‘932 Patent invalid because:
    a. the patent specification is insufficient;
    b. the claims are ambiguous;
    c. claims 1, and 7 to 43 are broader than any invention made or disclosed; or
    d. the promised utility of the invention was neither demonstrated nor soundly predicted as of the relevant date?

The ‘898 Patent:

1. Are claims 2, 4 to 26, and 28 irrelevant for failing to relate to a claim for the medicinal ingredient, the formulation, the dosage form, or the use of the medicinal ingredient?
2. Does APO-Dasatinib infringe the ‘898 Patent?
3. Is the ‘898 Patent invalid because:
    a. the claims are ambiguous;
    b. claims 4, 5, 9, and 10 claim ineligible subject matter;
    c. each of claims 1 to 18 is broader than any invention made or disclosed;
    d. the patent specification is insufficient;
    e. the promised utility of the invention claimed was neither demonstrated nor soundly predicted as of the filing date;
    f. the invention claimed was obvious or obvious to try;
    g. each of the claims is encompassed by the ‘932 Patent (double patenting);
    h. the invention claimed is anticipated by PTC Publication No. WO 2000/052778 (the “‘778 Application”);
    i. the ‘898 Patent does not meet the criteria of a selection patent?

[6] At the hearing the issues were narrowed to the following specific validity issues relating to three claims being asserted by the Applicants as being valid and infringed:

A. Is claim 27 of the ‘932 Patent invalid because:

    1. the promised utility of the invention was neither demonstrated nor soundly predicted as of the relevant date; or

    2. the disclosure is insufficient?

B. Is claim 1 or claim 3 of the ‘898 Patent invalid because:

    1. the invention disclosed was obvious or obvious to try; or

    2. the invention disclosed is encompassed by the ‘932 Patent (double patenting)?

B. *Burden of Proof*

[7] The Applicants bear the legal burden to establish on a balance of probabilities that all the allegations of invalidity asserted are not justified (*Abbott Laboratories v Canada (Minister of*

Health), 2007 FCA 153 at paras 9 to 10; *Hoffman-La Roche Ltd v Apotex Inc*, 2013 FC 718 at paras 58 to 61).

C. *Results*

[8] The results of this action are as follows:

A. The Respondent's allegation that claim 27 of the '932 Patent is invalid is justified because the Applicants did not:

    1. establish that the promised utility of the invention was demonstrated or soundly predicted as of the relevant date.

    The allegation of insufficiency is not justified.

B. The Respondent's allegation that claims 1 and 3 of the '898 Patent are invalid is justified because the Applicants did not:

    1. prove that the invention was not obvious to try; and
    2. show that claims 1 and 3 were not invalid due to double patenting.

II. Background

A. *Chronic Myelogenous Leukemia ("CML")*

[9] CML is a cancer affecting the blood, which comprises 15-20% of adult leukemias. In CML, there is an overproduction of myeloid-derived white blood cells and blasts within the bone marrow and blood.

[10] CML is the result of a translocation between chromosomes 9 and 22, creating what is known as the "Philadelphia chromosome". The translocation results in a fusion gene, BCR-ABL, which is not present in normal cells. The BCR-ABL gene makes the protein tyrosine kinase ("PTK") Bcr-Abl.

[11] PTKs are a large and diverse group of proteins within cells that phosphorylate tyrosine amino acid residues on other proteins within a cell. PTKs are grouped into "families" depending on the structural similarity between each protein. PTKs within the same family will have similar structures, while PTKs from different families may have very different structures.

[12] Tyrosine phosphorylation is commonly associated with a number of different cellular functions, including cell division and cell survival. Regulated cell division and survival are both important to the homeostasis of the hematopoietic system, and abnormal PTKs, such as Bcr-Abl, which constantly send signals for cells to grow, divide, and survive, can lead to disease.

[13] In CML, Bcr-Abl abnormally signals CML cells to produce too many white blood cells that do not die at a normal rate. Over time, these cells build up in the bone marrow so that there is less room available for healthy blood cells to grow.

[14] CML has three phases: (1) the initial chronic phase; (2) the accelerated phase; and (3) the final phase, in which CML has transformed into acute leukemia.

B. *Treatment of CML in the early 2000s*

[15] In 2000, the two standard treatments for CML were interferon (IFN-alpha) and hydroxyurea. Both treatments lead to severe side effects, and neither of these treatments were a cure for CML, which could only be accomplished through a stem cell transplant. At this time, it was well known that Bcr-Abl was the main driver of CML.

[16] In 2001, a drug called imatinib (also known as GLEEVEC®, and by the designation STI571) was approved by the United States Food and Drug Administration for the treatment of CML. Imatinib was understood to inhibit Bcr-Abl activity by binding to the kinase domain and inhibiting its ability to phosphorylate tyrosine residues, essentially turning off its unregulated signal. As a result, the CML cancer cells stop proliferating and eventually die. However, similar to interferon and hydroxyurea, imatinib is not curative of CML.

C. *Emergence of resistance to imatinib therapy*

[17] By 1999-2000, it was known that some patients were developing resistance to imatinib treatment. Often these patients had a mutation in Bcr-Abl at the site to which imatinib binds. The cells containing this mutation would not be affected by imatinib, and would continue to proliferate, eventually out-populating cells that did not contain the mutated Bcr-Abl. Other mechanisms of resistance were also known, such as over-expression of Bcr-Abl, which required a high dosage of imatinib to treat.

[18] The development of imatinib-resistant CML highlighted the need for additional and/or alternative therapeutic approaches to the treatment of CML.

III. The Applicants' Expert Witnesses

A. *Dr. Moshe Talpaz*

[19] Dr. Talpaz is the Alexander J. Trotman Professor of Leukemia Research at the University of Michigan. He also serves as the Associate Director of Translational Research at the University of Michigan Cancer Center and Professor of Internal medicine at the Department of Medicine at the University of Michigan.

[20] Dr. Talpaz obtained a MD from the Hadassah Medical School of Hebrew University in Jerusalem, Israel. He completed his residency at Kaplan Hospital, and a fellowship in developmental therapeutics and immunology at the University of Texas MD Anderson Cancer

Center. He joined the faculty of the University of Texas MD Anderson Cancer Center in 1981, and subsequently became a tenured, full professor and chair of the Bioimmunotherapy Department. In 2006, he joined the University of Michigan faculty.

[21] Dr. Talpaz has authored or co-authored over 450 journal articles and textbook chapters on CML. He is a member of the American Society of Hematology and is board certified in internal medicine and medical oncology. He is an expert in the area of hematologic malignancies, such as CML.

[22] Between 2003 and 2006, Dr. Talpaz was one of two international principal investigators leading the phase I clinical trial of dasatinib for Bristol-Myers Squibb Company ("BMS") (Charles Sawyers at the University of California Los Angeles was the second principal investigator). The Respondent points out that Dr. Talpaz failed to disclose (1) the fact that he had received funding from BMS at different times between 2003 and 2016; and (2) the fact that he has sat and currently sits on *ad hoc* advisory boards for BMS. I do not find this allegation to be of any consequence in this proceeding.

[23] Dr. Talpaz is an expert in CML, and therapeutics development for CML and imatinib-resistant CML.

B. *Dr. Mark P. Wentland*

[24] Dr. Wentland is a Professor Emeritus in the Department of Chemistry and Chemical Biology at Renssalaer Polytechnic Institute, Troy, NY ("Renssalaer"). Prior to becoming a Professor Emeritus, he was a full professor at Renssalaer.

[25] Dr. Wentland obtained a B.Sc. in chemistry from Central Connecticut State University, in 1966; and a Ph.D. in organic chemistry from Rice University, in 1970. From 1970-1994 he was employed at the Sterling-Winthrop Research Institute (now a part of Sanofi S.A.), as well as at Renssalear. He has authored over 70 peer-reviewed research articles and five reviews/book chapters. He is also an inventor on 32 United States Patents.

[26] Dr. Wentland is an expert in medicinal chemistry, particularly in the area of structure activity relationships and characterization of therapeutic compounds.

C. *Dr. Joel Barrish*

[27] Dr. Barrish is the Vice-President of Discovery Chemistry at BMS. He is a named inventor on both the '932 and '898 Patents.

[28] Dr. Barrish obtained a B.A. in chemistry from the University of Pennsylvania, in 1979; and a Ph.D. in organic chemistry from Columbia University in January 1983. Prior to joining BMS in 1988, he worked as a senior scientist at Hoffman-LaRoche. While at BMS he has led

teams that have advanced more than 20 compounds into clinical development, including SPRYCEL®.

[29] Dr. Barrish is an expert in drug development at BMS.

D. *Dr. Francis Lee*

[30] Dr. Lee is the Director of Tumor Pharmacology and Experimental Therapeutics at BMS. He is a named inventor on the ‘898 Patent.

[31] Dr. Lee obtained a B.Sc. in pharmacology from the University of Leeds, in 1980; a M.Sc. in radiation biology from the University of London, in 1981; and a Ph.D. in the Medical Research Council Clinical Oncology and Radiotherapeutics Unit at the University of Cambridge, in 1985. He completed a post-doctoral fellowship at the University of Rochester Cancer Center, in 1987, and became an assistant professor at the University of Rochester. In 1992, Dr. Lee started working at BMS as a Research Investigator.

[32] Dr. Lee is an expert in drug development at BMS.

E. *Dr. William L. Jorgensen*

[33] Dr. Jorgensen is a Sterling Professor at Yale University, and holds a Whitehead Professorship.

[34] He obtained an A.B. in chemistry from Princeton University, in 1970; and a Ph.D. in chemical physics from Harvard University in 1975. Prior to accepting his position at Yale in 1990, he was a professor in the Department of Chemistry at Purdue University.

[35] Dr. Jorgensen is or has been the editor of several scientific journals. He has published more than 400 peer-reviewed articles. He has also been awarded numerous honours recognizing his contributions to the field of chemistry, particularly computational chemistry.

[36] Dr. Jorgensen is an expert in the development and application of computational tools to facilitate drug discovery.

IV. The Respondent's Expert Witnesses

A. *Dr. B. Douglas Smith*

[37] Dr. Smith is a Professor of Oncology at the Johns Hopkins University School of Medicine, and serves on the active staff of the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins.

[38] Dr. Smith obtained an A.B. in Biology from Lafayette College, in 1987; and a M.D. from the Medical College of Pennsylvania, in 1992. He completed an internship and a residency in Medicine at the Strong Memorial Hospital, in Rochester, New York, between 1992 and 1994. He was the Chief Resident, Medicine, at the Strong Memorial Hospital in 1994-1995; and he

completed an Oncology Fellowship at Johns Hopkins University, in 1998. Since completing his Oncology Fellowship, he has taught and worked at Johns Hopkins University.

[39] Dr. Smith has published over 120 peer-reviewed articles, and has written over 40 book chapters and/or editorials. He has been recognized for his teaching, and is a member of numerous professional societies.

[40] Dr. Smith is an expert in the treatment of patients with hematologic malignancies, and the treatment of patients with acute myeloid leukemia, CML, and myelodysplastic syndrome.

B. *Dr. Thomas E. Smithgall*

[41] Dr. Smithgall is the William S. McEllroy Professor and Chair of the Department of Microbiology and Molecular Genetics at the University of Pittsburgh School of Medicine.

[42] Dr. Smithgall obtained a B.A. in biochemistry, in 1981; and a Ph.D. in pharmacology from the University of Pennsylvania School of Medicine, in 1986. From 1986-1990, he completed post-doctoral training first in the Department of Pharmacology, University of Pennsylvania School of Medicine and, subsequently, at the Laboratory of Biological Chemistry, National Cancer Institute, National Institutes of Health. Prior to joining the faculty at the University of Pittsburgh School of Medicine, in 1998, he was an assistant professor at Georgetown University School of Medicine, and then the University of Nebraska Medical Center.

[43] Dr. Smithgall has published over 130 peer-reviewed papers, and has written 21 reviews and/or book chapters. He is a named inventor on two United States Patents, one United States Provisional Patent, and one PTC application. He has been recognized for his research, and is a member of numerous professional and scientific societies.

[44] Dr. Smithgall is an expert in PTK structure and function, particularly the Src-family of PTKs.

V. The '932 Patent

A. *The Patent*

[45] The '932 Patent is a Patent Cooperation Treaty ("PCT") application entitled "Cyclic Protein Tyrosine Kinase Inhibitors", and has an international filing date of April 12, 2000; a publication date of October 26, 2000; and was issued on August 25, 2009. It has a US priority date of April 15, 1999; and its national entry into Canada was October 9, 2001.

[46] The '932 Patent relates to cyclic compounds and salts thereof, to methods of using such compounds in treating protein tyrosine kinase-associated disorders such as immunologic and oncologic disorders, and to pharmaceutical compositions containing such compounds.

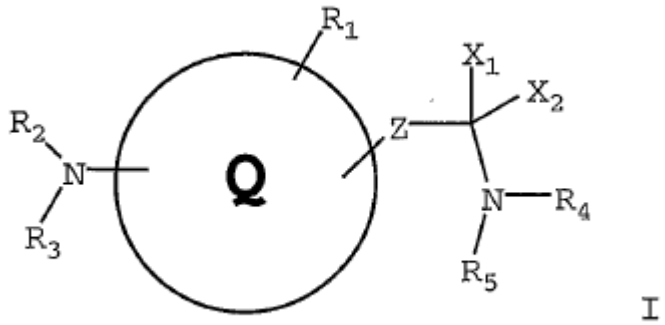
[47] The Background to the Invention states:

> Enhanced activity of PTKs has been implicated in a variety of malignant and non-malignant proliferative diseases. In addition, PTKs play a central role in the regulation of cells of the immune system. PTK inhibitors can thus impact a wide variety of oncologic

> and immunologic disorders. Such disorders may be ameliorated by selective inhibition of a certain receptor or non-receptor PTK, such as Lck, or due to the homology among PTK classes, by inhibition of more than one PTK by an inhibitor.

[48] The Summary of the Invention states:

> The present invention provides cyclic compounds of the following formula I and salts thereof, for use as protein tyrosine kinase inhibitors:



I

Where Q, Z, X1, X2, R1, R2, R3, R4, and R5 are described in detail on pages 3 to 8 of the patent specification.

[49] The '932 Patent describes Schemes A through E, and I through XI, for the preparation of the compounds of formula I, and states that "solvents, temperatures, pressures, and other reaction conditions may readily be selected by one of ordinary skill in the art".

[50] The '932 Patent has a lengthy Utility section, which in part reads:

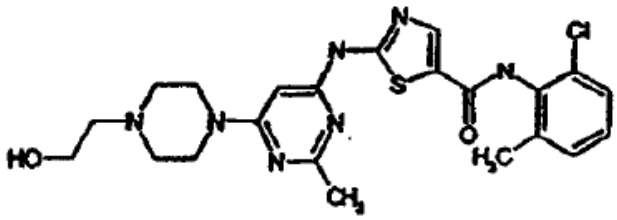
> The compounds of the present invention inhibit protein tyrosine kinases, especially Src-family kinases such as Lck, Fyn, Lyn, Src, Yes, Hck, Fgr, and Blk, and are thus useful in the treatment, including prevention and therapy, of protein tyrosine kinase-associated disorders such as immunologic and oncologic disorders. The compounds inhibit also receptor tyrosine kinases including HER1 and HER2 and are therefore useful in the treatment of proliferative disorders such as psoriasis and cancer. The ability of

> these compounds to inhibit HER1 and other receptor kinases will also permit their use as anti-angiogenic agents to treat disorders such as cancer and diabetic retinopathy. "Protein tyrosine kinase-associated disorders" are those disorders which result from aberrant tyrosine kinase activity, and/or which are alleviated by the inhibition of one or more of these enzymes.
>
> …
>
> Use of the compounds of the present invention in treating protein tyrosine kinase-associated disorders is exemplified by, but is not limited to, treating a range of disorders such as: [list of at least 30 disorders, including transplant rejection; T-cell mediated hypersensitivity diseases; Addison's disease; and] cancers, including cancers where Lck or other Src-family kinases such as Src are activated or overexpressed, such as colon carcinoma and thyoma, and cancers where Src-family kinase activity facilitates tumor growth or survival…
>
> The compounds of the formula I may be administered by any suitable means, for example, orally, such as in the form of tablets, capsules, granules or powers; sublingually; buccally; parenterally …
>
> The compounds of the present invention may be employed alone or in combination with each other and/or other suitable therapeutic agents useful in the treatment of protein tyrosine kinase-associated disorders such as PTK inhibitors other than those of the present invention, antiinflammatories (*sic*), antiproliferatives, chemotherapeutic agents, immunosuppressants, anticancer agents and cytotoxic agents.
>
> …

[51] The '932 Patent teaches five assays that were used to test the compounds enumerated in the claims: (1) enzyme assays using Lck, Fyn, Lyn, Hck, Fgr, Src, Blk, or Yes; (2) enzyme assays using HER1 or HER2; (3) cellular tyrosine phosphorylation cell assays; (4) calcium cell assays; and (5) cell proliferation assays. It also contains a list of 580 exemplary compounds that can be created from formula I. However, there is neither a list of specific compounds that were tested using each assay, nor any resultant data.

[52] There are 43 claims in the ‘932 Patent. The parties have agreed that only independent claim 27 is at issue in this action.

[53] Claim 27 states:

> The compound
>
> 
>
> or a salt thereof.

[54] Claim 35 contains the same chemical formula disclosed in claim 27, and states:

> Use of a compound or salts thereof for the treatment of cancer…

[55] Claims 36 to 43 depend on claim 35, and claims 37 to 43 disclose the use of the chemical compound in claim 35 for the treatment of gastric cancer, breast cancer, colon carcinoma, colorectal cancer, lung cancer, non-small cell lung cancer, and ovarian cancer.

B. *The Relevant Date*

[56] The relevant date for assessing whether there was sufficient disclosure and whether utility had been demonstrated is the claim date of the patent, which in this case is the priority date: April 15, 1999.

C. *The Persons of Ordinary Skill in the Art (POSITA)*

[57] The experts generally agreed on who the POSITA would be for both the ‘932 and ‘898 Patents. They stated the POSITA would not be a single person, but rather a team of skilled people, who together have the skills needed to read and understand the BMS Patents.

[58] Dr. Talpaz stated that the skilled team would be collectively versed in the fields of medicinal chemistry, biochemistry, pharmacology, biology, as well as clinical medicine. He opined that the skilled team would include medical doctors having specialties or training and experience in each of the diseases in the claims.

[59] Dr. Wentland was asked to assume that the POSITA had the following characteristics: a medicinal chemist with an advanced degree in medicinal chemistry or synthetic organic chemistry, with experience in pharmacology and biochemistry; who works with someone having an advanced degree in molecular biology or medicine, with education or experience in the field of cellular signal transduction.

[60] Dr. Smith expressed his opinion that the skilled addressee would be a team of individuals that would include chemists, who would make the compounds and formulations described in the patent; biochemists with experience in testing kinases; pharmacologists, who would be involved in assessing the properties of the compounds; and clinicians who would be involved in studying their use in the of treatment of the indicated conditions. The biochemists and pharmacologists on the team would have backgrounds or experience in oncology, or preferably CML. The clinicians

would have received specialized training in oncology, and experience in the treatment of blood cancers, such as CML and other forms of leukemia.

[61] Dr. Smithgall substantially agreed with Dr. Smith's definition of the POSITA, adding that the non-clinician members of the team would have a high level of training, most likely doctorate degrees and post-doctoral training. They would also have some experience with the diseases contemplated in the BMS Patents.

[62] Having considered the evidence before the Court, I find that the POSITA for the BMS Patents would be a team of skilled persons—who all have graduate level training (e.g. doctoral or post-doctoral training); or medical doctorates, with specialties in oncology or CML—including chemists, biochemists, pharmacologists, and clinicians.

D. *Common General Knowledge as of April 15, 1999*

(1) Preparation and testing of the compounds in the BMS Patents

[63] The BMS Patents presume that the POSITA would be able to select solvents, temperatures, pressures, and other reaction conditions in order to prepare the compounds of the formula I. Further, all of the experts agreed that the POSITA would know how to conduct screens to analyze the potency of small molecule compounds against PTKs. They also agreed that the POSITA would be able to run these assays in a high density format, which would allow for the testing of many compounds, compound concentrations, or enzyme targets simultaneously.

VI. Validity of the ‘932 Patent

A. *Utility*

(1) Law

[64] The *Patent Act,* section 2, defines an “invention” as something that is, amongst other criteria, “new and useful”. Justice Binnie, in *Apotex Inc v Wellcome Foundation Ltd,* 2002 SCC 77 at paragraph 46, [*Wellcome AZT*], stated that the inventor must “establish the utility as of the time the patent is applied for, on the basis of either demonstration or sound prediction”. If the patent is subsequently challenged and it is found that “the prediction at the date of application was not sound, or, irrespective of the soundness of the prediction, ‘there is evidence of lack of utility in respect of some of the area covered’” then the patent will be found invalid (*Wellcome AZT*, above, at para 56).

[65] The doctrine of “sound prediction” is premised upon balancing the public interest in early disclosure of inventions, before their utility has been verified by tests, and the public interest in avoiding granting monopoly rights in exchange for misinformation (*Wellcome AZT* at para 66). The public is entitled to obtain a solid, meaningful teaching in exchange for the patent rights granted to the inventor (*Wellcome AZT* at para 69, 83). Therefore, sound prediction is neither speculation nor lucky guesswork, even if it afterwards turns out of be correct (*Wellcome AZT* at para 84).

[66] The level of disclosure required by the doctrine of sound prediction is to be assessed as a function of the POSITA's knowledge, and as a function of what the POSITA would understand as a logical line of reasoning (*Bell Helicopter Textron Canada Limitée v Eurocopter, société par actions simplifée,* 2013 FCA 219 at para 152 [*Eurocopter*]). Where sound prediction is "reliant on data which does not form part of the common general knowledge, then disclosure in the specification may indeed be required to support a sound prediction" (*Eurocopter*, above, at para 153).

[67] The predictability of a particular result will depend on the evidence, and the soundness of the prediction is a question of fact (*Wellcome AZT* at para 71). In *Wellcome AZT*, at paragraph 70, Justice Binnie laid out three requirements for sound prediction :

1) There must be a factual basis for the prediction.
2) The inventor must have at the date of the patent application an articulable and "sound" line of reasoning from which the desired result can be inferred from the factual basis.
3) There must be proper disclosure. However, it is generally not necessary for an inventor to provide a theory of why the invention works.

[68] A sound prediction requires that there be a factual basis that would lead to a *prima facie* reasonable inference of utility (*Eli Lilly Canada Inc v Novopharm Limited*, 2010 FCA 197 at para 85). The inventor has the burden of disclosing both the factual basis and the line of reasoning, which bridges the gap between the factual basis and the predicted utility of the patent, in the patent specification, since it is he or she that will benefit from the monopoly (*Apotex Inc v Pfizer Canada Inc*, 2011 FCA 236 at paras 44, 52).

[69] An inventor does not need to describe the utility of his invention in his patent; however, if he does so, he will be held to the promise which he has made (*Sanofi-Aventis v Apotex Inc*,

2013 FCA 186 at para 48 [*Sanofi Plavix*]). If there is no explicit promise of a specific result, the test of utility is a "mere scintilla" of utility; however, if there is an explicit promise, then utility will be assessed by reference to the terms of the explicit promise (*Sanofi Plavix,* above, at para 49). An inventor can promise more for his or her invention than required by the *Patent Act*, so as to render the otherwise valid patent invalid (*Sanofi Plavix* at para 54).

[70] Whether or not the patent contains a specific promise is a matter of construction for the Court (*Sanofi Plavix* at para 50). To establish the content of the promise, the Court must not use inference, but rather should look for clear unambiguous language in the specification (*Sanofi Plavix* at para 66; *Eli Lilly Canada Inc v Hospira Healthcare Corporation,* 2016 FC 47 at para 41). Where the patent can be reasonably read as excluding a promise, the patent will be construed in favour of the patentee (*Apotex Inc v Pfizer Canada Inc,* 2014 FCA 250 at paras 66 to 67).

[71] Finally, it is settled law that some promises can impose an overarching utility requirement over all of the claims in the patent, while other promises may only affect a certain subset of the claims, and that inutility must then be assessed on a claim-by-claim basis (*Astrazeneca Canada Inc v Apotex Inc,* 2015 FCA 158 at paras 4 to 5).

(2) Analysis

[72] The Applicants assert that there is no explicit promise contained in the '932 Patent and, as such, the standard for determining utility is a "mere scintilla". They argue that the utility of the '932 Patent is only that the compounds disclosed are PTK inhibitors. Further, they submit

that there is no unequivocal promise that all of the compounds, including dasatinib, inhibit both Src-family PTKs and receptor PTKs, including HER1 and HER2.

[73] A fair construction of the ‘932 Patent, according to the Applicants, would preclude an overarching promise of therapeutic utility that touches claim 27. They argue that any therapeutic utility only attaches to particular embodiments of the invention, which are associated with the specific claims disclosing use for the treatment of disease (e.g., claims 35-43).

[74] The Applicants also contend that the Respondent cannot rely on the evidence of Dr. Smithgall because his approach to construing the patent to determine whether or not there was a promise was flawed. Particularly, they state that Dr. Smithgall was told to treat all assertions in the patent as promises, and not told to consider the claims in determining what promises were made.

[75] The Applicants state that there was demonstrated utility of claim 27 (i.e., dasatinib) at the filing date of the ‘932 Patent, because dasatinib was shown to inhibit the PTKs Lck and Yes. Further, if there is an explicit promise that dasatinib inhibits both the Src-family PTKs and HER1/HER2, which they deny, they assert that inhibition of HER1 and HER2 was soundly predicted at the filing date based upon the structural similarities of the inhibitors.

[76] Finally, the Applicants argue that the Respondent cannot now resile from the position taken in the ‘932 NOA that the skilled person “would not know whether each of the individual compounds of the invention was being promised as an inhibitor of all PTKs or specific PTKs …

all PTK-associated disorders or only certain PTK-associated disorders". That is, because that the Respondent admits in the '932 NOA that the POSITA would not know what the promise entailed, there can be no explicit promise.

(a) *The '932 NOA*

[77] Whether or not there is a promise contained in a patent is a matter of construction for the Court. However, the NOC process is such that the NOA must raise all of the legal and factual arguments, which the party crafting the NOA will rely upon, and subsequently introducing new facts and arguments is improper (*Bayer Inc v Cobalt Pharmaceuticals Co*, 2013 FC 1061 at para 37, aff'd in 2015 FCA 116; *Aventis Pharma Inc v Mayne Pharma (Canada Inc)*, 2005 FCA 50 at para 25).

[78] The Respondent rejects the assertion that they are estopped by way of the '932 NOA from arguing that the '932 Patent contains an explicit promise of utility on the basis that the passage relied upon by the Applicants in the '932 NOA should be read in the context of an "in the alternative" argument.

[79] The Respondent argues that it is clear in the '932 NOA that it has alleged that the inventors made the following unequivocal assertions as to what the compound disclosed in claim 27 of the '932 Patent would do:

1) Inhibit PTKs, especially Src-family kinases, and thus be useful in the treatment, including prevention and therapy of PTK-associated disorders such as immunologic and oncologic disorders; and
2) Inhibit also receptor tyrosine kinases, including HER1 and HER2, and thus be useful in treating proliferative disorders, such as psoriasis and cancer.

[80] I agree with the Respondent. The passage relied upon by the Applicants, at page 56 of the '932 NOA, indicates that the Respondent is making an alternative argument, which posits that the Court has accepted their overbreadth and ambiguity arguments (no longer live issues at the time of the hearing):

> For the reasons described above in respect of *Overbreadth* and *Ambiguity*, the skilled person reading the 932 Patent would not know whether each of the individual compounds of the invention was being promised as an inhibitor of all PTKs or specific PTKs. Likewise, the skilled person reading the 932 Patent would not know whether each of the compounds of the invention was being promised as being useful in the treatment of all PTK-associated disorders or only certain PTK-associated disorders. As discussed above, if it was the intention of the inventors that each compound of the invention was only being promised to inhibit a single PTK or a group of PTKs, or to be useful in the treatment of a single PTK-associated disorder or a group of PTK-associated disorders, this information has not been provided in the '932 Patent.

(b) *Promise of the Patent*

[81] The Applicants assert that there is no overarching promise that the compounds inhibit all PTKs and all receptor tyrosine kinases because a POSITA would think that conclusion to be scientifically absurd. Similarly, they contend that there is no promise that the compounds will inhibit both some non-receptor PTKs (e.g., the Src-family) and some receptor tyrosine kinases (e.g., HER1 and HER2). The Applicants also submit that, because the '932 Patent has claims that are separated into compound claims, use claims, and pharmaceutical composition claims, there can be no overarching promise of therapeutic utility. Further, they argue that "the potential utility of the compounds as therapeutics is explicitly disclosed in the '932 Patent as being ancillary to their utility as PTK inhibitors".

[82] The Respondent, in the ‘932 NOA, states that the promised utility of the subject matter claimed by the ‘932 Patent would be understood to include therapeutic use (‘932 NOA at 54):

> … that the compounds of the invention are PTK inhibitors, and that as a consequence of being PTK inhibitors, the compounds of the invention will be useful in the treatment of PTK-associated disorders such as immunologic and oncologic disorders.
>
> … the ability of the compounds of the invention to inhibit tyrosine kinases including HER1 and HER2 and, as a consequence, to be useful in the treatment of proliferative disorders such as psoriasis and cancer, and, in respect of the compound’s ability to inhibit HER1, to be useful in the treatment of angiogenic disorders such as cancer and diabetic retinopathy.

[83] Contrary to the Applicants’ assertions, there are clear references in the specification that support the view that there is an overarching promise of utility: the Field of the Invention, and the Utility section.

[84] The Field of the Invention states:

> The present invention relates to cyclic compounds and salts thereof, to methods of using such compounds in treating protein tyrosine kinase-associated disorders such as immunologic and oncologic disorders, and to pharmaceutical compositions containing such compounds.

[85] The Utility section contains the following statements:

> The compounds of the present invention inhibit protein tyrosine kinases, especially Src-family kinases such as Lck, Fyn, Lyn, Src, Yes, Hck, Fgr, and Blk, and are thus useful in the treatment, including prevention and therapy, of protein tyrosine kinase-associated disorders such as immunologic and oncologic disorders.
>
> The compounds inhibit also receptor tyrosine kinases including HER1 and HER2 and are therefore useful in the treatment of proliferative disorders such as psoriasis and cancer. The ability of

> these compounds to inhibit HER1 and other receptor kinases will also permit their use as anti-angiogenic agents to treat disorders such as cancer and diabetic retinopathy.
>
> …
>
> The present invention thus provides methods for the treatment of protein tyrosine kinase-associated disorders, comprising the step of administering to a subject in need thereof at least one compound of the formula I in an amount effective therefor.
>
> …
>
> Use of the compounds of the present invention in treating protein tyrosine kinase-associated disorders is exemplified by, but is not limited to, treating a range of disorders such as: [list of disorders including cancers where Src-family kinases are activated or overexpressed]
>
> …
>
> In a particular embodiment, the compounds of the present invention are useful for the treatment of the aforementioned exemplary disorders irrespective of their etiology …

[86] Dr. Smithgall testified that a POSITA would understand that the overarching promise of the ‘932 Patent was to (1) inhibit protein tyrosine kinases, especially Src-family kinases; (2) inhibit receptor tyrosine kinases, including HER1 and HER2; and (3) be useful to treat protein tyrosine kinase-associated disorders or useful as anti-angiogenic agents.

[87] On cross-examination, Dr. Smithgall admitted that he was not given any instructions regarding how to read the ‘932 Patent and legally assess utility. The Applicants assert that this makes Dr. Smithgall’s testimony unreliable. The Respondent argues that, while it did not fully instruct Dr. Smithgall on the law of utility, it asked Dr. Smithgall to determine if the ‘932 Patent made “explicit, unequivocal assertions (i.e. promises) as to what the compounds of claims 7 and

27 will do". Dr. Smithgall's opinion regarding the promise of the patent remained consistent throughout his cross-examination.

[88] Dr. Jorgensen opined that Dr. Smithgall's construction of the promise was incorrect, because the POSITA would think that it was scientifically absurd that a compound would inhibit all PTKs and receptor tyrosine kinases. He states that a POSITA would read the '932 Patent and conclude that the only expectation was that a compound would inhibit at least one PTK or receptor tyrosine kinase. Dr. Smithgall agreed that a POSITA would not expect each compound to inhibit all of the PTKs. However, he contended that the promise, as he understood it, was that each compound would inhibit both the Src-family PTKs and HER1/HER2, and that a POSITA would think this promise was scientifically reasonable.

[89] Dr. Jorgensen also testified that, because the tests disclosed in the '932 Patent are limited to *in vitro* assays, therapeutic utility is not promised. Additionally, he focused on statements containing the words "implicated" and "may" in the Background of the Invention, suggesting that the skilled person would not have understood that therapeutic use was an overarching promised because of those statements.

[90] However, Dr. Jorgensen's understanding of what the assays indicate is at odds with the fact that evidence of utility does not need to be disclosed within the patent. Justice Donald Rennie, when faced with a similar assertion in *Astrazeneca Canada Inc v Apotex*, 2014 FC 638 at paragraphs 127 to 130, stated that this type of approach to the promise of the patent, exemplified

by Dr. Jorgensen's reasoning, is tautological, contrary to the policy objectives of patent law, and would perversely encourage patentees to over-promise. I agree.

[91] Further, Dr. Jorgensen's focus on statements from the Background of the Invention indicates that he did not take into account the entire specification when assessing the promise of the invention. On cross-examination, Dr. Jorgensen explained that it was his belief that patent drafters in the early 2000s commonly employed language such as "are therefore useful" to mean "that there was hope that these compounds will prove to be useful in the treatment of disease". As such, I prefer the evidence of Dr. Smithgall, and I agree that Dr. Smithgall's interpretation of which receptors any given compound would inhibit is reasonable based upon the language of the specification.

[92] Additionally, after reading the entire specification, I find that this case is distinguishable from other cases where it was found that each different type of claim had different promised utilities, such that therapeutic utilities were operative for some claims and not others.

[93] For example, in *Apotex Inc v Pfizer Canada Inc*, 2013 FC 141 [*Apotex Imatinib*], Justice Judith Snider was asked to construe the promise of a patent which disclosed that the compounds in question will inhibit the protein kinases PKC, PDGF-R, or ABL and "can be used, for example," as anti-tumoral drugs. In a manner analogous to the '932 Patent, the claims of the *Apotex Imatinib* patent are broken down into compound claims, use claims, process claims, and medicament claims.

[94] Justice Snider found that the words “can be used” meant that the compounds have merely the potential, demonstrated or predicted, to be used for therapeutic purpose (*Apotex Imatinib,* above, at paras 139 to 151). Therefore, the therapeutic purpose was not part of the overarching promise of the patent, but only a promise associated with the use claims, which explicitly stated that the compounds could be used to treat atherosclerosis and for the chemotherapy of tumours (*Apotex Imatinib* at paras 177 to 180).

[95] In the ‘932 Patent, the language used in the specification is not equivocal in the same manner as the *Apotex Imatinib* patent (i.e., “can be used”). There are numerous instances in the Utility section where the inventors have stated that the compounds “are” useful for treatment of disease. Therefore, I find that there is an overarching promise of the patent for therapeutic utility against PTK-associated disorders, in addition to the specific therapeutic utilities disclosed in the use claims.

[96] Finally, the Applicants’ construction of the utility of the ‘932 Patent as having primary and ancillary utilities was not supported by any evidence, and is incorrect because it is based upon a reading down of the patent, such that there are primary and ancillary utilities.

[97] For these reasons, I conclude that there is a promised utility of the ‘932 Patent, which is as follows:

1) For all of the claims, the promise is that the compounds will inhibit both a Src-family PTK and HER1/HER2, and be therapeutically useful in treating a PTK-associated disorder or useful as anti-angiogenic agents.
2) For claims 35 to 43, the promise is that dasatinib will be useful to treat cancer, or the specified type of cancer.

(c) *Sound Prediction of Utility*

[98] There is no dispute that the inventors had not demonstrated the promised utility as of the filing date of the ‘932 Patent. Further, the Respondent contends that, if the overarching promised utility of the ‘932 Patent included the promise that the compounds will be useful for treatment of PTK-associated disorders, this utility was not soundly predicted in the ‘932 Patent. The Applicants have produced no evidence to challenge this allegation. However, they assert that, should the Court find that the overarching promised utility is that each of the compounds taught in the ‘932 Patent will inhibit both Src-family PTKs and HER1/HER2 (i.e., there is no overarching therapeutic utility), then the utility of dasatinib was soundly predicted.

[99] Since I found that the overarching promised utility included a promise that the compounds would be useful for treating PTK-associated disorders or as anti-angiogenic agents, and the Applicants do not challenge the allegation that there was no sound prediction of therapeutic utility for dasatinib, the Respondent’s allegation of inutility is justified. However, should I be incorrect in finding an overarching promise of therapeutic utility, such that the overarching promised utility is only that the compounds of the ‘932 Patent will inhibit both a Src-family PTK and HER1/HER2, I would still find that the Respondent’s allegation of inutility is justified for the reasons that follow.

[100] The Applicants submit that the inventors had shown that dasatinib could inhibit Src-family PTKs through testing against Lck and Yes, and could have soundly predicted that

dasatinib would also inhibit HER1/HER2, because of the structural similarities between dasatinib and other HER1/HER2 inhibitors.

[101] Dr. Smithgall stated that, at the relevant date, while a POSITA would reasonably expect that a compound that inhibited one Src-family kinase would inhibit the other Src-family kinases, it was not reasonable to believe that HER1 and HER2 would also be inhibited, and vice versa. He explained that the Src-family kinases are structurally similar in their kinase domains—likewise HER1 and HER2 are similar to each other—but the Src-family kinases and HER1/HER2 are, and were known at the time to be, structurally different.

[102] Dr. Jorgensen agreed that there are structural differences between the Src-family kinases and HER1/HER2. However, he testified that a POSITA would reasonably expect that dasatinib would provide some degree of inhibition against HER1/HER2, based upon the structure activity relationship data available from other inhibitors of HER1/HER2, some of which are disclosed in claim 7.

[103] In particular, he stated that the inhibition of HER1/HER2 is mediated by the interaction of a chloromethylphenyl group on the compound, which is found in dasatinib. He also asserted that the chemical substituents that make dasatinib different from the other compounds which were shown to inhibit HER1/HER2 are solvent exposed and, therefore, not relevant for binding and inhibition. This hypothesis has since been verified by BMS scientists, including Dr. Barrish and Dr. Lee, who published a paper in 2004 showing that dasatinib inhibited HER1 and HER2.

Therefore, in his opinion there was a sound prediction of utility, meeting the overarching promise in the ‘932 Patent.

[104] Dr. Smithgall disagreed with Dr. Jorgensen for three reasons:

1) there is a difference between some inhibition and useful inhibition for therapeutic use, and the POSITA would not be able to predict that there was useful HER1/HER2 inhibition;
2) the data shows that differences in the potentially solvent exposed substituents create a seven-fold and fourteen-fold difference in inhibitory activity (HER1 and HER2, respectively), and the POSITA would not know where or whether dasatinib would fall within that range; and
3) whether dasatinib has solvent exposed substituents, which do not interact with HER1 and HER2, is only a theory posited by Dr. Jorgensen and, even if correct, there is no indication that this was posited by the inventors at the relevant date.

[105] On cross-examination, Dr. Smithgall admitted that the difference between some inhibition and useful inhibition was related to whether the compounds to be used to create a practical drug to treat humans, not whether there was inhibition. Thus, his first two objections to Dr. Jorgensen’s conclusions are not relevant to the utility analysis. However, his third objection is pertinent to the sound prediction analysis.

[106] Based upon the evidence of the experts, it is not clear that, at the relevant date, the inventors had observed that HER1/HER2 inhibiting compounds all contained the common chloromethylphenyl group. Therefore, the Applicants have not demonstrated that the inventors had a factual basis for believing that dasatinib would inhibit HER1 and/or HER2.

[107] Further, as stated by Dr. Smithgall, there is no indication in the patent that the inventors thought that certain substituents were solvent exposed when interacting with HER1 and/or

HER2, which could lead them to posit that the differences between dasatinib and other compounds that bind HER1 and HER2 were irrelevant. As such, there was no sound line of reasoning that could have lead them to infer that dasatinib would inhibit HER1 and/or HER2.

[108] Therefore, I find that the Applicants have not proven that the inventors had, at the relevant date, a factual basis and a sound line of reasoning for believing that dasatinib would inhibit HER1 and HER2, and there was no disclosure of either the factual basis or a sound line of reasoning.

[109] Therefore, I find that, on a balance of probabilities, the inventors did not soundly predict that dasatinib would inhibit HER1 and HER2, in addition to the Src-family PTKs.

(3) Conclusion on Utility

[110] In summary on this question, I find that the Respondent's allegations of inutility are justified. There is an overarching promise in the '932 Patent that promises that dasatinib (claim 27) will:

1) inhibit a Src-family PTK;
2) inhibit HER1 and HER2; and
3) be useful to treat PTK-associated disorders or useful as an anti-angiogenic agent.

[111] The Applicants had the data to show that dasatinib would inhibit Src-family PTKs, but they did not have the data to show that dasatinib would inhibit HER1/HER2 and be useful to treat PTK-associated disorders or as an anti-angiogenic agent. Additionally, the Applicants did not prove that they had a factual basis or a sound line of reasoning to predict that dasatinib would

inhibit HER1/HER2 and be useful to treat PTK-associated disorders or as an anti-angiogenic agent.

[112] Therefore, the Applicants have not met the burden to show that the entire overarching promised utility was either demonstrated or soundly predicted at the relevant date, in respect of claim 27, for the ‘932 Patent.

B. *Sufficiency*

(1) Law

[113] The “patent bargain” underlying the patent system is embodied in the *Patent Act*. The disclosure requirements for the specification are found in section 27(3):

> (3) The specification of an invention must:
>
> (a) correctly and fully describe the invention and its operation or use as contemplated by the inventor;
>
> (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 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;
>
> (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
>
> (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.

[114] In *Consolboard Inc v MacMillan Bloedel (Sask) Ltd*, [1981] 1 SCR 504 at 520 [*Consolboard*], Justice Dickson, writing for the Supreme Court of Canada, discussed what the specification must contain in order to meet the disclosure requirements:

> In essence, what is called for in the specification (which includes both the "disclosure", i.e. the descriptive portion of the patent application, and the "claims") is a description of the invention and the method of producing or constructing it, coupled with a claim or claims which state those novel features in which the applicant wants an exclusive right. The specifications must define the precise and exact extent of the exclusive property and privilege claimed…
>
> We must look to the whole of the disclosure and the claims to ascertain the nature of the invention and methods of its performance … being neither benevolent nor harsh, but rather seeking a construction which is reasonable and fair to both patentee and public.

[115] Justice LeBel, in *Teva Canada Ltd v Pfizer Canada Inc*, 2012 SCC 60 at paragraph 50 [*Teva Sildenafil*], summarized Justice Dickson's reasoning as "the nature of the invention must be disclosed and … the entire specification, including the claims, must be considered in determining the nature of the invention and whether disclosure was sufficient".

[116] Each patent must contain only one invention, but will not be found invalid based solely on the reason that it has more than one invention (*Patent Act*, section 36(1)). Therefore, each claim is not to be construed as a separate invention in every case (*Teva Sildenafil*, above, at para 60). In the case of an invention relating to the use of a series of compounds, the inventive concept is the series of compounds for the use disclosed in the specification (*Teva Sildenafil* at para 66).

[117] *In Pioneer Hi-Bred Ltd v Canada (Commissioner of Patents)*, [1989] 1 SCR 1623 at 1638, Justice Lamer reiterated "the 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 a situation with cascading pharmaceutical claims, the disclosure in the specification and claims must "enable the public 'to make the same successful use of the invention as the inventor could at the time of his application'", it is not sufficient if "the skilled reader must undertake a minor research project to determine which claim is the true invention" (*Teva Sildenafil* at para 74).

[118] Although the POSITA knows that when a patent contains cascading claims, "the useful claim will usually be the one at the end concerning an individual compound", claims that include compounds that do not work will be deemed invalid by the Court (*Teva Sildenafil* at para 80).

(2) Analysis

[119] The Respondent's insufficiency argument is made in the alternative, premised upon the Court finding that there is no overarching promise of utility in the '932 Patent. As discussed above, I have found that there is an overarching promise for the claims, including claim 27. Therefore, I do not find it necessary to deal with the Respondent's sufficiency allegations in detail.

[120] However, had I not made the above utility determination, and given the common general knowledge at the relevant date and the nature of the testing required to determine which PTKs

are inhibited by dasatinib (i.e., routine tests, which are disclosed in the specification)—I would find that the ‘932 Patent specification is sufficient.

VII. The ‘898 Patent

A. *The Patent*

[121] The ‘898 Patent is a PCT application entitled “Oral Administration of Cyclic Protein Tyrosine Kinase Inhibitors” and has an international filing date of March 23, 2004; a publication date of October 7, 2004; and was issued on July 10, 2012. It has a US priority date of March 24, 2003; and its national entry into Canada was September 21, 2005.

[122] The ‘898 Patent relates to cyclic compounds and salts thereof, and to methods of using such compounds in treating PTK-associated disorders such as immunologic and oncologic disorders, and to pharmaceutical compositions containing such compounds.

[123] The Background of the Invention states:

> Enhanced activity of PTKs has been implicated in a variety of malignant and non-malignant proliferative diseases. In addition, PTKs play a central role in the regulation of cells of the immune system. PTK inhibitors can thus impact a wide variety of oncologic and immunologic disorders. Such disorders may be ameliorated by selective inhibition of a certain receptor or non-receptor PTK, such as Lck, or due to the homology among PTK classes, by inhibition of more than one PTK by an inhibitor.

[124] The Summary of the Invention and the Methods of Preparation sections are substantially the same as the '932 Patent. Similar to the '932 Patent, the '898 Patent has a lengthy Utility section, which is substantially the same as in the '932 Patent; differences include:

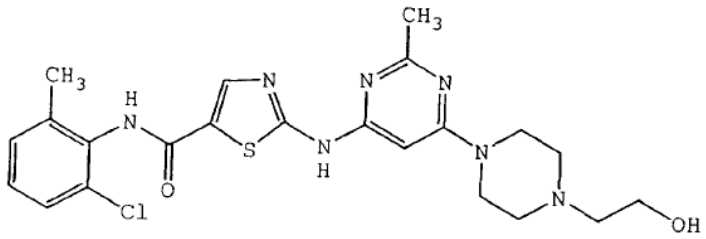
> The compounds of the present invention are useful for the treatment of cancers such as chronic myelogenous leukemia (CML), gastrointestinal stromal tumor (GIST), small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC), ovarian cancer, melanoma, mastocytosis, germ cell tumors, acute myelogenous leukemia (AML), pediatric sarcomas, breast cancer, colorectal cancer, pancreatic cancer, prostate cancer and others known to be associated with protein tyrosine kinases such as, for example, SRC, BCR-Abl and c-KIT. The compounds of the present invention are also useful in the treatment of cancers that are sensitive to and resistant to chemotherapeutic agents that target BCR-Abl and c-KIT, such as, for example Gleevec® (STI-571).

[125] The '898 Patent contains the same 580 example compounds that are listed in the '932 Patent.

[126] The '898 Patent has 30 claims, and the parties have agreed that claims 1 and 3—which disclose the use of dasatinib for the treatment of CML and imatinib-resistant CML, respectively—are the only claims at issue in this action.

Claim 1:

> Oral use for treating cancer of a compound of formula IV or a salt thereof:



> wherein the cancer is chronic myelogenous leukemia (CML).

Claim 2:

> Oral use in the manufacture of a medicament for treating cancer of…
>
> [Same chemical compound disclosed in claim 1]
>
> wherein the cancer is chronic myelogenous leukemia.

Claim 3:

> The use of claim 1 or 2, wherein the chronic myelogenous leukemia (CML) is resistant to STI-571.

B. *The Relevant Date*

[127] The relevant date for determining whether the ‘898 Patent is obvious is the priority date: March 24, 2003.

C. *POSITA*

[128] As discussed above, the POSITA for the ‘898 Patent would be the same as for the ‘932 Patent.

D. *Common General Knowledge as of March 23, 2003*

[129] Justice Johanne Gauthier, in *Eli Lilly & Co v Apotex Inc*, 2009 FC 991, affirmed in 2010 FCA 240, at paragraph 97, articulated the following about common general knowledge:

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

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

(1) Src-family PTKs and imatinib-resistant CML

[130] Dr. Talpaz stated that the POSITA would know that imatinib (GLEEVEC®) was the leading CML treatment, in 2003, and that patients were becoming resistant to it. At the relevant date, imatinib resistance was a major concern, and there was a significant need for and push towards a therapeutic that had the ability to treat imatinib-resistant CML.

[131] A POSITA would know that imatinib is not classified as a Src-family kinase inhibitor, and that Bcr-Abl, which it inhibits, is not a member of the Src family. Additionally, a POSITA would understand that a compound that was shown to inhibit a particular PTK would not necessarily inhibit PTKs belonging to a different family, and that the only way to know which PTKs would be inhibited would be to conduct testing. The POSITA would know that the compound code for imatinib was STI-571, and that STI-571 also inhibits several other kinases, including c-KIT and PDGF-R.

[132] Dr. Talpaz further opined that the only PTK inhibitors demonstrated to be useful for the treatment of CML, at the relevant date, were Bcr-Abl inhibitors, and that the research into PTKs for the treatment of CML was focused mainly on inhibiting Bcr-Abl because of its direct

relationship with CML. He asserted that the POSITA would have attributed the effect of both SKI-606 and PP1, two PTK inhibitors mentioned in the Apotex NOAs, on CML tumors to their ability to inhibit Bcr-Abl, rather than their ability to inhibit Src-family kinases. He also opined that the POSITA would have known that human clinical testing was necessary to determine whether compounds were suitable for oral administration, particularly for CML, the cells of which have a complex relationship with their cellular environment.

[133] Dr. Talpaz also asserted that, before March 24, 2003, it was only a theory that some Src-family PTKs were overexpressed in CML, and that the inhibition of these PTKs may play a role in the treatment of CML and imatinib-resistant CML. He stated that, "to this day, no non-BCR-Abl (sic) PTK inhibitor has ever been demonstrated to be effective as a treatment for CML". Further, he opined that most research groups, including that of Dr. Charles Sawyers, were focused on mechanisms of resistance that were dependant on Bcr-Abl. However, he admitted in his affidavit that, at the time, researchers had proposed that some resistance may be related to the binding of imatinib to another protein, or an overabundance of certain Src-family kinases, such as Lyn and Hck.

[134] The prior art shows that, in fact, his research team had postulated that Src-family kinases were implicated in imatinib-resistance. However, he asserted that this theory was "extremely controversial at the time" and that there was no consensus in the scientific community over the role of the Src-family kinases. Additionally, he stated that "any potential therapies based on these theories would not have been self-evident for the oral treatment of CML or CML resistant to GLEEVEC® at the relevant date".

[135] Dr. Talpaz opined that the papers discussing the possible role of Src-family kinases are cautious in their discussions about the role of these PTKs in CML. These papers use phrases such as:

> … the results presented in the paper suggest that GLEEVEC® resistance is mediated by mechanisms other than BCR-Abl and that targeted inhibition of the Src family kinase, LYN may circumvent GLEEVEC® resistance but that additional studies were required…
>
> We are fully aware that our data did not formally prove the inhibition of Src kinases as the sole or major explanation for the Abl-unrelated biologic effects observed.
>
> … future work is needed to address the role that Src kinases play in CML progression *in vivo* and the effects of Src inhibition on Bcr-Abl signaling and oncogenic activity in a whole animal model of CML.

[136] He concluded that, at the relevant date, the POSITA would not have expected that a Src-family kinase inhibitor would be effective for the treatment of CML or imatinib-resistant CML.

[137] Dr. Smith agreed with Dr. Talpaz that it would have been a part of the common general knowledge that imatinib resistance existed. However, he opined that it was known that imatinib resistance occurred through different mechanisms than just Bcr-Abl mutations, including secondary pathways believed to be involved in CML. These pathways include the Src/Lyn pathway as well as the Jak and Stat pathways.

[138] He stated that the POSITA would know that Src was part of the Bcr-Abl pathway. He disagreed with Dr. Talpaz that it was only theoretical that the Src-family of kinases played a role in the development of cancer and imatinib resistance. Dr. Smith conducted a PubMed search (i.e.

a search in a widely used life sciences database) and found 87 papers addressing the relationship between the PTKs Bcr-Abl and Scr. From there, he chose 11 papers that were of particular value to a scientist/clinician working on imatinib-resistant CML. He opined that the POSITA would have been aware of these papers. Five of these 11 papers are alleged to be prior art in the '898 NOA.

[139] Dr. Smith further asserted that, while Dr. Talpaz is correct that there had not been any human clinical trials involving Src-family kinase inhibitors by the relevant date, this does not mean that the role of Src-family kinases in the treatment of CML had not been established. Dr. Smith opined that Dr. Talpaz was mistaken that it was part of the common general knowledge that the use of Src-family PTK inhibitors was controversial, and considered to be a less successful line of research.

[140] On cross-examination, Dr. Smith admitted that there were a number of lines of research that were being followed at the time, a few of which were reasonably advanced with regards to finding a therapeutic. However, he testified that it would be incorrect to say that those lines of research were better or more well-known than the research into the use of Src-family kinase inhibitors to treat CML.

[141] Further, he disagreed with Dr. Talpaz's interpretation of the language used in the academic literature relating to Src-family kinases and imatinib-resistant CML. He contended that it would be common general knowledge that the terms "suggest", "may", or the suggestion that "further work is required" are common scientific parlance that do not signify that the author is

uncertain or particularly cautious about the implications of their results. He stated that it is known and understood by anyone who publishes that peer-reviewed journals generally do not allow papers to be published containing statements that imply that their interpretations of results are fact.

[142] Dr. Smithgall opined that it was known by the mid-1990s that Bcr-Abl does not act alone as the driver of CML, and that there was an "explosion of interest" in the use of kinase inhibitors in treating CML and other cancers. He contended that, by the early 2000s, it was part of the common general knowledge that Bcr-Abl recruits members of the Src-family, particularly Lyn and Hck, amplifying the signal for cell proliferation that is transmitted by Bcr-Abl and accelerating the development of CML.

[143] He agreed with Dr. Talpaz that the POSITA would have known that a common cause of imatinib-resistance is mutation in Bcr-Abl; however, he disagreed that scientists were focusing primarily on this mechanism of resistance. He stated that, at the relevant time, scientists had begun to target the accessory kinases that are part of the Bcr-Abl pathway. For, example his laboratory had been exploring Src-family PTKs as alternative targets for CML therapy.

[144] Dr. Smithgall agreed with Dr. Smith that it was common knowledge, by March 2003, that Src-family PTK inhibitors in combination with Bcr-Abl inhibitors could be used to treat CML, although no treatment had been established in human clinical trials. He also agreed with Dr. Smith that targeting Src-family PTKs was non-controversial, and something a POSITA would have been aware of, at the relevant date.

[145] He disagreed with Dr. Talpaz that that research relating to the roles of other PTKs in CML was widely criticised at the time. He stated that he was actively involved in the field of research and does not recollect any such criticism. Dr. Smithgall also opined that it was common knowledge, by March 2003, that several Src PTK inhibitors inhibited Bcr-Abl. Further, Dr. Smithgall stated that it would have been part of the common general knowledge that dual inhibitors of Src-family PTKs and Bcr-Abl were able to kill some imatinib-resistant cells.

[146] Dr. Smithgall also performed a PubMed search to find scholarly papers that a POSITA would have considered to be prior art. He came up with a final list of 13 papers that related to the interaction between Bcr-Abl and Src-family kinases, five of which are alleged to be prior art in the '898 NOA. Finally, he agreed with Dr. Smith that the POSITA would have known that the cautious language in the scientific papers at the time was commonplace and that the POSITA would put more stock in the results that were presented than on the language in the paper.

(2) Conclusion to common general knowledge

[147] Based upon the expert evidence, I find that the common general knowledge of the POSITA with regards to the '898 Patent includes knowledge of the following:

1) the structural relationship between different PTKs, particularly, Bcr-Abl and the Src-family kinases;
2) the molecular causes of CML, and the mechanisms that cause imatinib-resistant CML;
3) how Src-family kinases interact with the Bcr-Abl pathway;
4) the existence of Src-/Bcr-Abl dual inhibitors; and
5) common avenues of research being pursued to develop treatments for imatinib-resistant CML, within the scientific community, including the use of Src-family kinase inhibitors as additional or alternative targets for CML therapy.

E. *Prior Art*

[148] The Respondent identifies seven key documents that it asserts form the prior art in considering the obviousness of the ‘898 Patent.

(1) PCT Application No. WO/2000/062778 (the “‘778 Application”)

[149] The ‘778 Application is the PCT application that led to the ‘932 Patent. It has an International Filing Date of April 12, 2000; and an international publication date of October 26, 2000. It is titled “[c]yclic protein tyrosine kinase inhibitors”, and describes a family of compounds, including 580 specifically exemplified compounds, that have been found to be inhibitors of PTKs, particularly Src-family PTKs. The ‘778 Application indicates that compounds inhibiting Lck, or other Src-family members, are useful in the treatment of cancers, where Src-family PTKs are overexpressed or where Src-family kinase activity facilitates tumor growth or survival.

[150] The ‘778 Application states that “[t]he compounds of the present invention inhibit protein tyrosine kinases, especially Src-family kinases such as Lck, Fyn, Lyn, Src, Yes, Hck, Fgr and Blk”, and that these compounds are “useful in the treatment, including prevention and therapy, of protein tyrosine kinase-associated disorders such as immunologic and oncologic disorders”.

[151] The Applicants argue that the Respondent did not prove that the ‘778 Application was publically available to the POSITA at the relevant date. The Respondent maintains that the ‘778

Application has an international publication date of October 26, 2000 and would have been publically available before March 24, 2003. I agree.

[152] The Applicants also object to the contents of the ‘778 Application being used as prior art because the Respondent has not provided evidence that it would have been found by the POSITA. In fact, Drs. Smith and Smithgall admitted, on cross-examination, that they had not performed searches in the patent literature, and were not aware that the ‘778 Application existed prior to the start of this action.

[153] However, the Respondent insists that a POSITA would have been able to find the ‘778 Application through a search of relevant patent databases, and that it is not germane that their experts did not search for the ‘778 Application themselves.

[154] The Federal Court of Appeal has held that prior art relevant for the purposes of assessing obviousness is limited to that which the POSITA “would locate conducting a reasonably diligent search” (*E Mishan & Sons Inc v Supertek Canada Inc*, 2015 FCA 163). Therefore, the Respondent is not limited only to the prior art found by its experts. Further, while it may be best practice when asking experts to opine on prior art or the common general knowledge to have them perform the necessary searches, the NOC process can constrain a respondent, who must ensure that all facts that they will rely upon at trial are part of the NOA; therefore, a respondent is likely to have curated the prior art before hiring experts.

[155] In this case, given that the ‘778 Application became the ‘932 Patent, which explicitly states that it discloses compounds to treat PTK-associated disorders such as oncologic disorders, I find, on a balance of probabilities, that a POSITA who performed a relevant patent database search would have found and identified this patent application as prior art.

(2) WO 03/013540 (the “‘540 Application”)

[156] The ‘540 Application is titled “[u]se of C-SRC inhibitors alone or in combination with STI571 for the treatment of leukemia”. It has an international publication date of February 20, 2003, and Dr. Talpaz is listed as one of the inventors.

[157] The ‘540 Application describes the use of c-Src inhibitors (i.e., cellular Src kinase inhibitors) alone or in combination with imatinib in the treatment of leukemia. The inventors state that they found that compounds inhibiting c-Src, or other Src-family kinases, were effective in treating leukemia, preferably CML, and that use of these compounds in combination with imatinib provides greater effects than either compound alone. The ‘540 Application also states that imatinib-resistant CML can be treated by a compound inhibiting c-Src, alone or in combination with imatinib.

[158] The Applicants raise the same arguments against including the ‘540 Application in the prior art as they do against the ‘778 Application.

[159] The ‘540 Application explicitly names both STI-571 (imatinib) and leukemia in its title, and has an international publication date prior to the relevant date. Therefore, I find, on a balance

of probabilities, that a POSITA searching a relevant patent database would find the ‘540 Application. As such, it is valid prior art with respect to the ‘898 Patent.

(3) Donato *et al. Blood*, 101: 690-698, 2003

[160] Donato *et al.* was published in January 2003, and is co-authored by Dr. Talpaz. In this paper, an imatinib-resistant CML cell line was prepared, in which the imatinib resistance was not caused by mutated Bcr-Abl, suggesting that Bcr-Abl was no longer coupled to the proliferation and survival of the cells. It was determined that the reason for imatinib resistance was the overexpression of the Src-family kinases, Hck and Lyn. The authors of the paper also found that there were patients whose imatinib-resistant CML was caused by a similar mechanism. They concluded that imatinib resistance may be mediated in part though the overexpression of other PTKs. This finding identified Lyn and Hck as targets for PTK inhibitors in treating imatinib-resistant CML.

(4) Stanglmaier *et al. Leukemia*, 17: 283-290, 2003

[161] Stanglmaier *et al.* was published in February 2003. This paper describes the interaction between Bcr-Abl with the Src-family kinase Hck, and demonstrated that Hck is involved in Bcr-Abl cell proliferation. This finding confirmed the finding in Lionberger *et al. Journal of Biological Chemistry*, 275: 18581-18585, 2000.

(5) Golas *et al. Cancer Research,* 63: 375-381, 2003

[162] Golas *et al.* was published in January 2003. It describes SKI-606, which is a dual Src-/Abl PTK inhibitor. The authors show that SKI-606 was able to inhibit the growth of CML cells in cell cultures and in a mouse model, following oral administration. The authors concluded that the simultaneous inhibition of Bcr-Abl and Src pathways could offer significant therapeutic advantages in patients.

(6) Warmuth *et al. Blood,* 101: 664-672, 2003

[163] Warmuth *et al.* was published in January 2003. This paper shows that compounds with dual activity against Src and Bcr-Abl are active against cells that express various imatinib-resistant mutants. The authors concluded that there is a role for dual-specific inhibitors in the treatment of leukemias, such as imatinib-resistant CML.

(7) Wilson *et al. Oncogene*, 21: 8075-8088, 2002

[164] Wilson *et al.* was published in November 2002, and is co-authored by Dr. Smithgall. The results of this study demonstrated that it was possible to stop the proliferation of CML cells by targeting Src kinases without also inhibiting Bcr-Abl. This paper also showed that Src kinases are alternative targets to Bcr-Abl for CML drug therapy, particularly in patients with imatinib-resistant CML.

VIII. Validity of the ‘898 Patent

A. *Obviousness*

(1) Law

[165] Justice Rothstein set out the four-part test for obviousness in *Sanofi-Synthelabo Canada Inc v Apotex Inc*, 2008 SCC 61 at paragraph 67 [*Sanofi-Synthelabo*]:

1) Identify the notional person skilled in the art and identify the relevant common general knowledge of that person.
2) Identify the inventive concept of the claim in question or if that cannot readily be done, construe it.
3) Identify what, if any, differences exist between the matter cited as forming part of the “state of the art” and the inventive concept of the claim or the claim as construed.
4) Viewed without any knowledge of the alleged invention as claimed, ask whether those differences constitute steps which would have been obvious to the person skilled in the art, or do they require any degree of invention.

[166] In areas where advances are often found through experimentation, the fourth part of the obviousness tests may be reframed as asking whether the experiments were “obvious to try”, using the following, non-exhaustive, factors (*Sanofi-Synthelabo*, above, at para 69):

1) Is it more or less self-evident that what is being tried ought to work, and/or are there a finite number of identified predictable solutions that would be known to persons skilled in the art?
2) What is the extent, nature, and amount of effort required to achieve the invention (i.e., is the experimentation prolonged and arduous, or are the trials routine)?
3) Is there a motive provided in the prior art to find the solution that the patent addresses?

[167] The reference for the test of obviousness is a technician, who is skilled in the art but possesses no scintilla of inventiveness or imagination (*Beloit Canada Ltd v Valmet OY* (1986), 8 CPR (3d) 289 at 294). Obviousness is a difficult test to meet, because it is necessary to show that the skilled person would have come directly and without difficulty to the invention (*Sanofi-*

Synthelabo at paras 71 and 85). However, the existence of multiple obvious routes to an invention does not necessarily render the route taken to be non-obvious (*Shire Biochem Inc v Canada*, 2008 FC 538 at para 80)

[168] Finally, the Court must assess obviousness keeping in mind that experts in the field may unknowingly be biased by hindsight (*Bridgeview Manufacturing Inc v 931409 Alberta Ltd (cob Central Alberta Hay Centre)*, 2010 FCA 188 at para 50).

(2) Analysis

[169] As discussed above, I have identified the POSITA and the relevant common general knowledge. Additionally, the Parties agree that the inventive concepts of claims 1 and 3 of the '898 Patent are the oral use of dasatinib for the treatment of CML, and oral use of dasatinib for the treatment of imatinib-resistant CML, respectively. Thus, to justify their allegation of obviousness, the Respondent must demonstrate that any difference between the state of the art and the invention was either obvious or obvious to try.

[170] The Applicants argue that the inventive concepts represented significant advancements in the field of CML treatment, and were the first treatment that could solve the problem of imatinib resistance. The Applicants further state that the use of Src-family PTK inhibitors to treat CML and/or imatinib-resistant CML was not the most obvious avenue of research, because CML treatment with Src-family PTK inhibitors was only a possibility. They assert that the Respondent steered its experts towards Src-family PTK solutions.

[171] Further, the Applicants submit that it was not obvious that dasatinib would be an effective oral treatment at the time, because no one knew that dasatinib would (1) be a Src-family PTK inhibitor and a sufficiently powerful inhibitor of the right PTKs; and (2) have the physiological properties required to produce a treatment effect in a CML or imatinib-resistant CML patient when administered orally. In particular, the Applicants contend that, without a clinical "proof of concept", the steps between the prior art and the '898 invention cannot be obvious or obvious to try.

[172] They assert that the BMS scientists carried out extensive work, over a period of years, including a clinical study in patients resistant or intolerant to imatinib, to discover that dasatinib would work as an oral therapeutic. Finally, they state that the fact that the Respondent had to mosaic together five scientific papers, the '778 Application, and the '540 Application to make its obviousness argument shows that the invention was nonobvious.

[173] Both Parties agree that it was not obvious at the relevant date that dasatinib would be an effective oral treatment for CML and/or imatinib-resistant CML. However, the Respondent contends that it would have been obvious for the clinician/scientist to try to improve on existing CML-therapies by administering a Src-family PTK inhibitor. Further, the Respondent argues that, because dasatinib was identified in the '778 Application as a PTK inhibitor that could be used for PTK-associated diseases, particularly cancer, dasatinib would have been an obvious candidate to try.

(a) *Claim 1: Treatment of CML*

[174] Both the ‘778 Application and the ‘540 Application teach that inhibitors of Src-family kinases can be used to treat PTK-associated cancers.

[175] The ‘778 Application discloses that the compounds taught (including dasatinib) “inhibit protein tyrosine kinases, especially Src-family kinases…” and, thus, are useful for the treatment of PTK-associated disorders, which result from aberrant tyrosine kinase activity, and/or which are alleviated by the inhibition of one or more PTKs. It further teaches that the compounds disclosed may be administered by any suitable means, including oral means. Similarly, the ‘540 Application discloses a method of treating a human having leukaemia, including CML, comprising administering at least one compound inhibiting the c-Src PTK.

[176] Dr. Smithgall testified that the POSITA knew at all times that CML was a tyrosine kinase-associated disorder, which he described on cross-examination as “any disease entity in which an enzyme or member of the enzyme family of protein tyrosine kinases would be disregulated or constitutively active, and thus making (sic) them potential targets for inhibition”. Both Drs. Smith and Smithgall stated that, in the early 2000s, there were labs actively researching the application of Src-family kinase inhibitors in the treatment of CML. These labs, including those that published the papers that are prior art to the ‘898 Patent had pre-clinical data demonstrating that the inhibition of Src-family PTKs would inhibit cell proliferation in CML models. Therefore, contrary to Dr. Talpaz’s contention that the ‘540 Application proposed a controversial line of thinking, Dr. Smithgall stated that the statements in the ‘540 Application

reinforced the POSITA's expectation that a Src-family PTK inhibitor, such as dasatinib, would treat CML.

[177] There was significant dispute over whether the '778 Application taught oral delivery of dasatinib or merely suggested the possibility of oral delivery. In the Utility section of the '778 Application, the inventors disclose that:

> The present invention also provides pharmaceutical compositions comprising at least one of the compounds of the formula I capable of treating a protein tyrosine kinase-associated disorder in an amount effective therefor, and a pharmaceutically acceptable vehicle or diluent. The compositions of the present invention may contain other therapeutic agents as described below, and may be formulated, for example, by employing conventional solid or liquid vehicles or diluents, as well as pharmaceutical additives of a type appropriate to the mode of desired administration (for example, excipients, binders, preservatives, stabilizers, flavors, etc.) according to techniques such as those well known in the art of pharmaceutical formulation.
>
> The compounds of the formula I may be administered by any suitable means, for example, orally, such as in the form of tablets, capsules, granules or powders; sublingually; buccally; parenterally …
>
> Exemplary compositions for oral administration include suspensions which may contain, for example, …; and immediate release tablets which may contain, for example, … The present compounds may also be delivered through the oral cavity by sublingual and/or buccal administration …
>
> (emphasis mine)

[178] Both Drs. Smith and Smithgall opined that the '778 Application taught oral administration of the formula I compounds. They asserted that a POSITA would have read both the '778 Application and the '540 Application, and understood that the inventors had obtained some data to support their assertions. On cross-examination, Dr. Smith stated that he did not

fully understand the chronology of reporting, presenting, and sharing data in the context of patents, and that he believed that a patentee would have data that had not shown up in the literature to support the claims in the patent. Dr. Smithgall, on cross-examination, admitted that it was his understanding that some, but not all, of the compounds of the ‘778 Application would be suitable for oral administration because conditions such as psoriasis, of which the ‘778 Application teaches treatment, would be unsuitable for treatment via oral administration.

[179] Dr. Talpaz, one of the inventors of the ‘540 Application, stated that an *a priori* expectation of success with respect to oral treatment would have been impossible given the pharmacokinetics and host factors relevant to CML. He contended that the POSITA could not have gleaned any information regarding the *in vivo* properties of either the compounds disclosed in the ‘540 Application or dasatinib, including how or if they would enter into CML cells, from the prior art. Therefore, he opined that a significant amount of clinical research would have had to be done to achieve the invention.

[180] However, during cross-examination about the ‘540 Application, Dr. Talpaz admitted that a POSITA would read statements made in a patent with the understanding that the patentee had either demonstrated the truth of the statement or had a basis from which to extrapolate its truth. Although he subsequently vacillated over what level of proof a POSITA would understand a patentee to have to support the extrapolation, and fixated on meaning of certain words (e.g., orally administered), he acknowledged that a skilled reader would rely on the statements made by the patentee and believe that they had some basis in fact.

[181] Although I agree with Dr. Talpaz that the effectiveness of oral administration could not be predicted prior to performing clinical tests, I do not consider this to be dispositive of whether an invention was obvious to try. The first question of the obvious try analysis asks if it is more or less self-evident that an approach ought to work, which is a question that is very similar to the question of sound prediction in the utility analysis. Many patents, including the ‘898 Patent, have been granted in the absence of clinical data at the claim date. If the utility of an invention can be predicted based upon pre-clinical data, the logical corollary is that a POSITA, having only pre-clinical information, could find the invention obvious to try, and in this case, given the common general knowledge, would have found that oral use of dasatinib to treat CML was obvious to try.

[182] Additionally, despite the fact that the Applicants argue that a significant amount of research was involved in creating an oral treatment using dasatinib, the ‘898 Patent does not disclose any teachings regarding oral administration over and above that which is taught in the ‘778 Application. Nor does the ‘898 Patent disclose any information with regard to the bioavailability of dasatinib. As such, the ‘898 Patent relies upon the same description of the invention as does the ‘778 Patent.

[183] Subsection 27(3)(a) of the *Patent Act* states that the specification of an invention must “correctly and fully describe the invention and its operation or use as contemplated by the inventor”. If the oral use of dasatinib is correctly and fully described in the ‘898 Patent, then it follows that the oral use of the formula I compounds (including dasatinib) was also disclosed in the ‘778 application. It is undisputed that statements made by the patentee, such as what constitutes prior art, are to be treated as binding admissions (see for example *Merck & Co Inc v*

Pharmascience Inc, 2010 FC 510 at para 8; *Eli Lilly Canada Inc v Novopharm Limited*, 2007 FC 596 at para 142; *Whirlpool Corp v Camco Inc* (1997), 76 CPR (3d) 150 at 186, aff'd 2000 SCC 67).

[184] Therefore, based upon the prior art, a POSITA at the relevant time would have known that dasatinib was a Src-family PTK inhibitor that had therapeutic value and could be administered orally, and that Src-family PTK inhibitors—particularly c-Src, Lyn, and Hck inhibitors—could be used to treat CML. Further, Dr. Smithgall testified that the Src-family PTKs are similar enough in structure such that a compound that inhibited one member of the family would inhibit other Src-family kinases. This evidence was not disputed by either Dr. Jorgensen or Dr. Talpaz. Thus, the POSITA could assume that dasatinib would inhibit the PTK c-Src, and other appropriate Src-family PTKs, based upon the '778 Application.

[185] The Applicants provided no evidence suggesting that the work they did to reach the invention in claim 1 (i.e., oral administration of dasatinib to treat CML) was long or arduous. There existed publically available CML cell lines and mouse models, and none of the experts suggested that the pre-clinical work, which was done prior to the relevant date, was anything but routine. Further, the '898 Patent shows and, on cross-examination, Dr. Talpaz agreed that no chemical modifications had to be made to dasatinib to make it a viable therapeutic. Dr. Smithgall opined that the POSITA would not require any inventive ingenuity to apply the information from the '778 Application and the prior art to conclude that it would be obvious to try to orally treat CML using dasatinib. Finally, as noted above, BMS had not commenced any of the clinical trial work by the priority date of the '898 Patent.

[186] In conclusion on the issue of claim 1, based upon the evidence given by the experts, I find that the Respondent's allegation that the claim is obvious is justified.

(b) *Claim 3: Treatment of imatinib-resistant CML*

[187] By early 2003 it was part of the common general knowledge that imatinib resistance was becoming a serious problem in the management of CML. As such, there was significant interest in finding alternative treatments that could be used in patients who had developed imatinib resistance.

[188] In cross-examination, Dr. Smith explained that there were multiple approaches to treating imatinib-resistant CML being explored in the scientific and medical community, including inhibiting farnesyl transferase, increasing the dose of imatinib, finding alternative Bcr-Abl inhibitors, and inhibiting Src-family PTKs. However, based upon the detailed summaries provided by Drs. Smith and Smithgall regarding their prior art searches, I find that the Respondent did not steer either expert towards prior art discussing the role of Src-family PTKs in imatinib-resistant CML.

[189] Dr. Smith testified that, of these approaches, the Src pathway was one of the most interesting and promising ways of tackling imatinib resistance, and that the other approaches did not have such an academic "track record", as of 2003. He explained that Src-family kinases are in the Bcr-Abl pathway, and that it was known, at the relevant time, that targeting the Bcr-Abl pathway was a successful means of inhibiting cell proliferation in imatinib-resistant CML studies.

[190] Dr. Talpaz asserted that the role of Src-family PTKs in CML was merely speculative as of March 2003, and suggested that the POSITA would not have thought that testing Src-family PTK inhibitors would be obvious to try. However, the prior art shows that clinician/scientists were interested in how Src-family PTK activity affected CML and imatinib-resistant CML cells. Further, the prior art shows that these clinician/scientists were persuaded, by the relevant date, that Src-family PTKs, particularly Lyn and Hck, were potential therapeutic targets for CML and imatinib-resistant CML.

[191] Dr. Talpaz insisted that the teachings in the ‘540 Application were just a disclosure of theoretical potential. Nonetheless, it would have motivated the POSITA to continue investigations into Src-family kinase inhibition, and led them to believe that there existed more data than was published to support the connection between Src-family kinase inhibition and CML treatment. Dr. Talpaz cannot now disavow the statements that were made in the ‘540 Application. The Court will not engage in redrafting prior art in an effort to uphold patents, regardless of whether subsequent evidence shows that the statements made in those preceding patents were potentially unwarranted.

[192] As discussed above, Drs. Smith and Smithgall opined that a POSITA would have believed that the ‘540 Application taught that compounds inhibiting Src-family kinases were effective in treating CML, reinforcing the scientific direction taught by the other prior art. In fact, Dr. Lee admitted, on cross-examination, that it was the links between Src-family PTKs and CML, which had been disclosed in the literature, that spurred his interest in testing Src-family

PTK inhibitors, particularly dasatinib, in imatinib-resistant cell lines. In his memorandum to BMS requesting that dasatinib be considered for clinical testing, dated July 2002, Dr. Lee wrote:

> The mechanistic basis for the ability of [dasatinib] to overcome Gleevec™ resistance is not well understood. Recent reports suggesting that the activation of two Src family members (Lyn and Hck) may be partially responsible for Gleevec™ resistance in CML patients supports the potential of [dasatinib] in the management of this disease.
>
> …
>
> There are currently no marketed Src inhibitors and therefore the utility of such an agent in the treatment of human malignancies has yet to be determined. However, the importance of the Src family protein kinases in the etiology of many forms of human cancer is well established.

[193] At the time of writing the memorandum, the evidence shows that Dr. Lee had preclinical data showing that dasatinib was curative in an imatinib-resistant cell line and a CML mouse model, as well as bioavailability and toxicity data in multiple animal models. In his affidavit, Dr. Lee described his process for creating imatinib-resistant cell lines; however, there is no description of any of the bioavailability or toxicity studies. The prior art shows that the method for making imatinib-resistant cell lines was part of the common general knowledge. Further, I infer from Dr. Lee's lack of commentary regarding the bioavailability and toxicity experiments that they were routine tests that required no inventive steps.

[194] Dr. Lee and his team received approval to put together a Phase I clinical trial, which started in November 2003. This evinces that BMS was sufficiently confident in the use of dasatinib, based on the pre-clinical data, to invest a significant amount of money in clinical

testing, and suggests that the Applicants thought that it was more or less self-evident that what was to be tried ought to work.

[195] Dr. Talpaz stated that it was his opinion that someone who did not have Dr. Lee's level of knowledge about dasatinib would not have chosen to test dasatinib over other Src-family PTK inhibitors that had been disclosed in the scientific literature. On cross-examination, Dr. Smith admitted that there were other Src-family PTK inhibitors being pursued as potential leads for CML treatment, such as PP1 and SKI-606; however, he maintained that dasatinib would have been of interest.

[196] The fact that there are multiple obvious routes towards an invention does not necessarily render any or all of them all non-obvious. This is particularly true given the methods through which scientists screen compounds for potential therapeutic activity. Dr. Lee explained that compound tests are done in a high-through put manner, such that hundreds of compounds can be screened against many cell lines or PTKs for activity on 96-well plates. Further, there was no evidence adduced from any of the experts suggesting that there existed prior art that taught away from the use of dasatinib to treat CML or imatinib-resistant CML. Thus, I do not agree that use of dasatinib for treating CML or imatinib-resistant CML was nonobvious, simply based upon the fact that there were other candidate compounds being investigated in the scientific literature.

[197] Dr. Talpaz testified that, to this day, there has not been any demonstration that an inhibitor that inhibits Src-family PTKs, and no other PTKs, is effective for the treatment of CML or imatinib-resistant CML. Further, Dr. Lee explained that his team had since found that

dasatinib treats CML and imatinib-resistant CML because it inhibits Bcr-Abl, in addition to Src-family PTKs. On cross-examination, Dr. Smithgall agreed that it was true that there was no evidence of an inhibitor that blocked only Src-family PTKs, and no others, being useful in treating CML or imatinib-resistant CML. However, he contended that did not negate the fact that the POSITA, at the relevant date, would have thought Src-family PTK inhibitors were candidate compounds that should work in treating CML and imatinib-resistant CML.

[198] Further, both Drs. Smith and Smithgall asserted that it was obvious to try to use dasatinib against both CML and imatinib-resistant CML. They explained that treatment of imatinib-resistant CML with Src-family PTK inhibitors was obvious because the inhibitor would be targeting an alternative kinase in the Src pathway, which is distinct from the mechanism of imatinib inhibition of Bcr-Abl, allowing treatment of both CML and imatinib-resistant CML via the same alternative mechanism.

[199] Finally, as discussed regarding claim 1, the oral use of Src-family PTK inhibitors, particularly dasatinib, was taught in the prior art. Therefore, based on the evidence of the experts, I find that the Respondent’s allegation of invalidity for obviousness with respect to claim 3 is justified.

(3) Conclusion Obviousness

[200] In conclusion on the issue of obviousness, I find that, as of March 2003, a POSITA would have understood the following:

1) Numerous *in vitro* and *in vivo* studies had shown a link between the Src-family PTKs—particularly Src, Lyn, and Hck—and CML, such that inhibition of a Src-family PTK was one of the most interesting and promising ways of tackling CML treatment and imatinib resistance.
2) *In vivo*, and at least pre-clinical, work had been done demonstrating that c-Src inhibitors could treat CML and imatinib-resistant CML, alone or in combination with imatinib.
3) Data existed showing that the compounds of formula I, disclosed in the '778 Application and including dasatinib, were appropriate for oral administration against PTK-associated disorders.

[201] The invention in claims 1 and 3 of the '898 Patent is the oral use of dasatinib for the treatment of CML and imatinib-resistant CML, respectively. It is clear that, at the relevant time, there was significant motivation in the field of CML research to find an alternative therapy for treating CML and imatinib-resistant CML. Given the state of the art prior to March 24, 2003, I find that the Respondent's allegation that it was more or less self-evident that trying to treat CML and imatinib-resistant CML with dasatinib ought to work is justified. Further, I find that the Respondent's allegation that the nature of the work required to achieve the invention was routine is justified.

[202] As such, I find that the Respondent's allegation of invalidity based upon obviousness to be justified for both claim 1 and claim 3.

B. *Double Patenting*

(1) Law

[203] Section 36(1) of the *Patent Act* states "[a] patent shall be granted for one invention only but in an action or other proceeding a patent shall not be deemed to be invalid by reason only that it has been granted for more than one invention". The patent bargain is in the interest of both the patentee and the public "only if the patent owner acquires real protection in exchange for disclosure, and the public does not for its part surrender a more extended monopoly than the statutory [20] years from the date of the patent grant" (*Whirlpool Corp v Camco Inc*, 2000 SCC 67 at para 37 [*Whirlpool*]).

[204] Double patenting occurs when two patents are issued to the same inventor, and the subsequent patent has identical claims to the first (*Whirlpool*, above, at para 63). Determining whether double patenting has occurred requires the Court to compare the claims, not the disclosures, of both patents and determine whether the patents are (1) "identical or coterminous"; or (2) obvious, such that the claims of the second patent are "not 'patentably distinct' from those of the earlier patent" (*Whirlpool* at paras 63 to 66).

[205] A second patent cannot be justified unless the claims exhibit novelty or ingenuity over the first patent (*Whirlpool* at para 67). Recently, Justice Pelletier, writing for the Federal Court of Appeal, stated that the date at which obviousness-type double patenting is to be analyzed remains an open question, and that there possibly existed alternate frameworks, which are not

dependent on a reference date, for approaching double patenting (*Apotex v Eli Lilly*, 2016 FCA 267 at paras 38 to 40 [*Apotex Tadalafil FCA*]):

> Furthermore, the issue of the comparison date in double patenting cases had not arisen previously in the Supreme Court jurisprudence, or in the works of the text book writers. It would be surprising, to say the least, if Binnie J. purported to deal with a novel question by implication … I can only conclude that Binnie J's reticence on the point was deliberate and that he did not intend to settle that particular question.
>
> …
>
> The fact that this issue has not arisen in this form in the past may be an indication that there may be other ways to approach it. Perhaps, the Court, having construed the claims of each of the patents with the assistance of the persons skilled in the art, simply compares the claims and decides whether the later claims are patentably distinct from the earlier claims on the basis of the insights which it has gained in the course of the construction of the patents… going forward, parties should not feel that they are locked into the framework chosen by the parties in these cases.

(2) Analysis

[206] At the hearing, the Parties agreed that if I found the Respondent's allegations of obviousness to be justified regarding claim 1 of the '898 Patent, then the Respondent's allegation of obviousness-type double patenting for the same claim would also be justified. As such, the only claim at issue with regards to double patenting is claim 3.

[207] There was significant argument over which date should be relevant to the double patenting analysis: the claim date of the first patent ("First Filing"), the priority date of the second patent ("Second Priority"), or the publication date of the second patent ("Second Publication"). If the relevant date is the First Filing date, then claim 3 would not be invalid for

obviousness-type double patenting, because imatinib-resistant CML was not well known as of April 15, 1999. However, if the relevant date is either the Second Priority date or the Second Publication date, then my finding that the Respondent's allegation that claim 3 is obvious is justified entails that claim 3 be invalid for obviousness-type double patenting.

[208] The Applicants argue that, absent clear direction from either the Federal Court of Appeal or the Supreme Court of Canada, it is appropriate for the Court to follow the decision of Justice Yves de Montigny in *Eli Lilly Canada Inc v Mylan Pharmaceuticals ULC*, 2015 FC 17 [*Mylan*], which was upheld on appeal (*Mylan v Eli Lilly*, 2016 FCA 119 [*Mylan FCA*]) without the Federal Court of Appeal making a determination as to which of the First Filing date or the Second Priority date was the appropriate date at which to assess obviousness-type double patenting.

[209] The Respondent argues that, based upon the evil of double patenting—which is to force the public to endure a prolonged monopoly on an invention—the date for assessing obviousness-type double patenting should be the Second Publication date. The Respondent asserts that this is the first date at which the patentee can enforce the second patent and the public is threatened by the risk of liability for infringement. In the alternative, the Respondent argues that the Second Filing date is the appropriate date at which to assess obviousness-type double patenting.

[210] In *Mylan*, Justice de Montigny stated that use of the Second Priority date would engender a fusion of the obviousness-type double patenting analysis and the pure obviousness analysis, and circumvent the timing requirements articulated in section 28.3 of the *Patent Act*. He

suggested that it would be inappropriate to "read into the claims of the first patent more than what would have been understood by the person skilled in the art at the claim date when comparing the claims of the second patent to those of the first patent" (*Mylan* at para 134).

[211] In *Mylan FCA* at paragraph 47, Justice Rennie did not explicitly endorse Justice de Montigny's choice of the First Priority date; but, he stated that he was "convinced that the publication date of the later patent (the last date) is not the appropriate one". However, Justice Pelletier, writing for the special panel of the Federal Court of Appeal constituted specifically to resolve the question of whether *Mylan FCA* followed the Supreme Court of Canada's decision in *Whirlpool*, stated (*Apotex Tadalafil FCA* at para 39):

> For these reasons, I do not agree that *Whirlpool* has decided that the date at which the claims of the two patents in issue in a double patenting case are to be compared is the publication date of the later patent. This remains an open question.

[212] Due to the facts of the case, Justice Pelletier determined that there was no reason for the Federal Court of Appeal to depart from the conclusion reached on the double-patenting issue in *Mylan FCA*, but he declined to affirm Justice Rennie's exclusion of the Second Publication date (*Apotex Tadalafil FCA* at para 41). Therefore, the law as it currently exists on the appropriate date for the obviousness-type double patenting analysis is inconclusive.

[213] In light of Justice Rennie's explicit comments regarding the suitability of the Second Publication date, I find that the Respondent's main submissions regarding the date, while persuasive based upon the principles underpinning obviousness-type double patenting, cannot succeed. However, I note that Justice Pelletier suggested an alternative framework for assessing

obviousness-type double patenting that appears to effectively place the date of the analysis at the Second Publication date, since claim construction is to be done as of the publication date of each patent (*Apotex Tadalafil FCA* at para 40):

> Perhaps, the Court, having construed the claims of each of the patents with the assistance of the persons skilled in the art, simply compares the claims and decides whether the later claims are patentably distinct from the earlier claims on the basis of the insights which it has gained in the course of the construction of the patents.

[214] In obviousness-type double patenting, the impermissible evergreening concerns the addition of non-inventive bells and whistles to the first patent. Assessing the whether or not the claims of the two patents are patentably distinct as of that earlier date would exclude amendments, particularly use amendments, that become obvious at a later date through the evolution of the common general knowledge. It would be idiosyncratic for a subsequent patent to be obvious when compared to the first, but not an example of obviousness-type double patenting.

[215] As such, I agree with the comments made by Justice Mary Gleason in *Eli Lilly Canada Inc v Apotex Inc*, 2015 FC 875 [*Eli Lilly Tadalafil*] at paragraph 132:

> Particularly in the context of pharmaceutical patents involving a new use for an existing compound or class of compounds, there could be a situation where the common general knowledge advances after the claim date of the first patent that would render the new use claimed in the second patent obvious as of the claim date in the second patent, resulting in the later patent being an impermissible evergreening through extension based on obvious amendments to the initial patent. In such circumstance, I believe a sound argument may be made for the selection of the priority date of the second patent as being the date in respect of which the assessment of obviousness-type double patenting should be undertaken.

[216] Based upon my finding that the Second Priority date is the appropriate date at which double patenting is to be analyzed, I find that the Respondent's allegations of double patenting are justified for both claim 1 and claim 3 of the '898 Patent.

IX. Costs

[217] Costs will follow the event, and are to be assessed at the middle of Column IV of Tariff B. Apotex is also entitled to be paid its reasonable disbursements, and applicable taxes. If the parties are unable to agree on costs, the parties may make submissions to the Court within two weeks of the date of this judgment.

JUDGMENT

THIS COURT'S JUDGMENT is that:

1. This application in respect of Canadian Patent Nos. 2,366,932 and 2,519,898 is dismissed.
2. Apotex's allegation of invalidity regarding claim 27 of the '932 Patent is justified because of inutility.
3. Apotex's allegation of invalidity regarding claims 1 and 3 of the '898 Patent is justified because of obviousness and double patenting.
4. Apotex shall have its costs of this application assessed at the middle of Column IV of Tariff B. If the parties cannot agree on a costs disposition, concise written cost submissions, not exceeding 5 pages in length, shall be submitted no later than 14 days of the date of this Judgment.
5. The protective order of Prothonotary Martha Milczynski, dated November 25, 2015, is continued. If the Minister of Health issues an NOC to Apotex for APO-Dasatinib, Apotex shall advise the Court within 48 hours of the issuance of the NOC to facilitate amendment to the Public Judgment and Reasons by removing redactions dealing with the contents of APO-Dasatinib.

"Michael D. Manson"
Judge

FEDERAL COURT

SOLICITORS OF RECORD

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