Federal Court  Cour fédérale

Date: 20180718

Docket: T-944-15

Citation: 2018 FC 754

Ottawa, Ontario, July 18, 2018

PRESENT: The Honourable Mr. Justice Locke

BETWEEN:

TEVA CANADA LIMITED

Plaintiff

and

JANSSEN INC. and MILLENNIUM PHARMACEUTICALS, INC.

Defendants

AND BETWEEN:

MILLENNIUM PHARMACEUTICALS INC., JANSSEN INC., CILAG GMBH INTERNATIONAL, CILAG AG and JANSSEN PHARMACEUTICA NV

Plaintiffs by Counterclaim

and

THE UNITED STATES OF AMERICA REPRESENTED BY THE DEPARTMENT OF HEALTH AND HUMAN SERVICES

Patentee added pursuant to s. 55(3) of the *Patent Act*

and

TEVA CANADA LIMITED

Defendant by Counterclaim

PUBLIC JUDGMENT AND REASONS
(Confidential Judgment and Reasons issued July 18, 2018)

I. Overview

[1] This action began as a claim by the plaintiff, Teva Canada Limited (Teva), against Janssen Inc. (Janssen) and Millennium Pharmaceuticals, Inc. (Millennium) for compensation under s. 8 of the *Patented Medicines (Notice of Compliance) Regulations*, SOR/93-133 [the *Regulations*] for losses suffered during the time that Teva was kept off the market for its version of a drug for treating cancer that is marketed in Canada by Janssen under the name Velcade. The active pharmaceutical ingredient is bortezomib. Teva's product is called Teva-bortezomib.

Because of Teva's recent amalgamation with Actavis Pharma Company (Actavis), it is also relevant to consider Actavis's product called Act-bortezomib.

[2] Janssen had rights in Canada to Canadian Patent Nos. 2,203,936 (the 936 Patent) and 2,435,146 (the 146 Patent). In 2012, it commenced two applications under the *Regulations* against Teva seeking orders prohibiting the issuance of a notice of compliance (NOC) to Teva until expiration of the 936 and 146 Patents, respectively. Millennium was named as a party in the applications, as owner of the 936 Patent and as licensee and sub-licensor of the 146 Patent.

[3] Both applications were dismissed by decisions of Justice Robert L. Barnes concluding that the claims in issue of each of the 936 and 146 Patents were invalid for obviousness. These decisions are cited as *Janssen Inc v Teva Canada Limited*, 2015 FC 247 and *Janssen Inc v Teva Canada Limited*, 2015 FC 184, respectively. Teva subsequently obtained its NOC and commenced the present action.

[4] Janssen and Millennium defended the present action on a number of grounds, including that Teva is not entitled to compensation because any sales it was prevented from making due to the delay in the issuance of its NOC would have been of products that infringed the 936 and 146 Patents, as well as Canadian Patent No. 2,738,706 (the 706 Patent). In addition, Janssen and Millennium, as well as Cilag GmbH International, Cilag AG and Janssen Pharmaceutica NV, counterclaimed against Teva seeking various remedies (including damages) for the alleged infringement of the 936, 146 and 706 Patents since Teva obtained its NOC.

[5] In its reply in the main action and in defence against the counterclaim, Teva denied infringement of the 936, 146 and 706 Patents and alleged, among other things, that all of the claims in issue are invalid.

[6] The parties have managed to reach agreement on a number of issues, including the quantum of any compensation or damages that may be payable. The parties have indicated that only the following issues remain in dispute:

1. With regard to the 936 Patent,
    a. Whether claims 37 and 69 are obvious;
2. With regard to the 146 Patent,
    a. What is the inventive concept, and
    b. Whether the asserted claims are obvious;
3. With regard to the 706 Patent,
    a. How the claims should be construed,
    b. Whether Teva-bortezomib infringes,
    c. Whether Act-bortezomib infringes, and
    d. Whether the asserted claims are obvious.

II. Background to the Patented Technologies

[7] As indicated, this case concerns three patents related to a treatment for certain blood cancers (multiple myeloma and mantle cell lymphoma) in respect of which the active molecule is bortezomib. Cancers are the result of an uncontrolled reproduction (proliferation) of mutated cells. Bortezomib, like many other cancer treatments, acts to limit this uncontrolled reproduction.

The following paragraphs provide a general description of bortezomib and how it works to treat cancer.

[8] Bortezomib is a boronic acid analog of a dipeptide. A peptide is a string of amino acids; a dipeptide comprises two amino acids. By comparison, a tripeptide comprises three amino acids and a tetrapeptide comprises four. An amino acid is composed of an amino group, a carboxyl group and a side chain, all bonded together. It is the side chain that gives each amino acid its distinctive characteristics. There are 20 natural amino acids, and many more unnatural amino acids. The amino acids in a peptide are often identified sequentially as P1, P2, P3 (if present), and so on. The P1 amino acid has a free carboxyl group and is referred to as the C-terminus. The last amino acid in the peptide has a free amino group and is referred to as the N-terminus.

[9] It is known to replace the carboxyl group of the P1 amino acid with something else. This produces what is called an amino acid analog. In the case of bortezomib, the carboxyl group is replaced by a boronic acid.

[10] There is no limit to the number of amino acids that can be strung together in a peptide. Longer peptides are called proteins. These can have hundreds and even thousands of amino acids.

[11] Reproduction of cells, whether cancer cells or normal cells, requires the breaking (or cleaving) of proteins. This is done using enzymes called proteases as catalysts. Each protease has a different chemical profile which favours it to react chemically with certain positions on certain

proteins to achieve the cleaving. The cancer treatment of relevance in this case involves inhibiting the function of one particular protease called the proteasome.

[12] The proteasome is a particularly complex protease that was discovered only in the late 1970s, and whose function remains somewhat mysterious because it does not behave consistently like any of the known classes of proteases. For a time, the proteasome was known as the multicatalytic protease because it has several different areas of activity.

[13] For many years, the proteasome was considered an atypical serine protease based largely on the knowledge that certain (but not all) classes of compounds known to inhibit proteases having a serine amino acid residue at the active site (serine proteases) were also effective at inhibiting the proteasome. However, Seemüller et al, "Proteasome from Thermoplasma acidophilum: a threonine protease" (1995) 268:5210 Science 579-582 revealed that the proteasome has a threonine amino acid residue at the active site, making it a threonine protease.

[14] One of the challenges in protease inhibition as a cancer treatment is to target cancer cells with maximum effect while minimizing the effect on healthy cells. There is little point in killing cancer cells in a patient if the patient's healthy cells are equally affected. The measure of the effect of a protease inhibitor is called potency. The characteristic of good potency against target cells while having minimal effect on non-target cells is called selectivity or specificity.

[15] Testing of potency *in vitro* is reported as K_i (the inhibitory constant). This reports the affinity of a molecule to the enzyme to be inhibited. The lower the K_i value, the greater the potency. Even where a compound is shown to be potent *in vitro*, its ability to penetrate a target

cell in order to reach the protease therein to be inhibited is not certain. This ability can be tested and the result is reported as IC_{50} (the half-maximal inhibitory concentration). Again, the lower the IC_{50} value, the greater the potency. Finally, even where a compound is shown to be potent and capable of penetrating a cell, it must be tested *in vivo*.

[16] The center of the function of a protease inhibitor is its "warhead". This is the location that is intended to bond chemically with the target protease and impede its protein-cleaving function. A cell that is unable to cleave proteins cannot clear the clutter of unwanted proteins. This can lead to the death of the cell. A cancer-treating peptide analog like bortezomib has a warhead accompanied by a particular sequence of amino acids chosen to facilitate chemical binding of the analog with the target protease.

[17] A last portion of a protease-inhibiting peptide analog is a protecting group, also known as a blocking group or capping group. It is located at the N-terminus and its function is to prevent the amino group of the last amino acid in the peptide string from inadvertently reacting with surrounding compounds and thereby changing its chemical make-up.

[18] I turn now to a description of the bortezomib molecule. Its chemical name is N-(2-pyrazine)carbonyl-L-phenylalanine-L-leucine boronic acid, and it is shown in Figure 1 below.

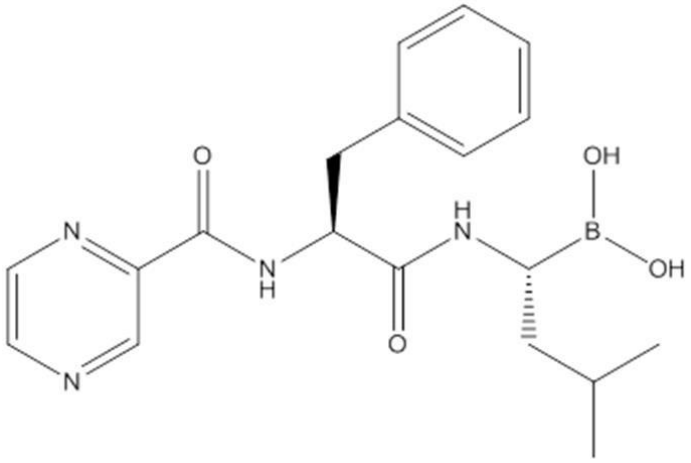


Figure 1

[19] Figure 2 below highlights P1 and the fact that the carboxyl group thereof is replaced with a boronic acid, which is identified with two OH groups bonded to a boron atom (shown as a small B within the molecule). The boronic acid is the warhead.

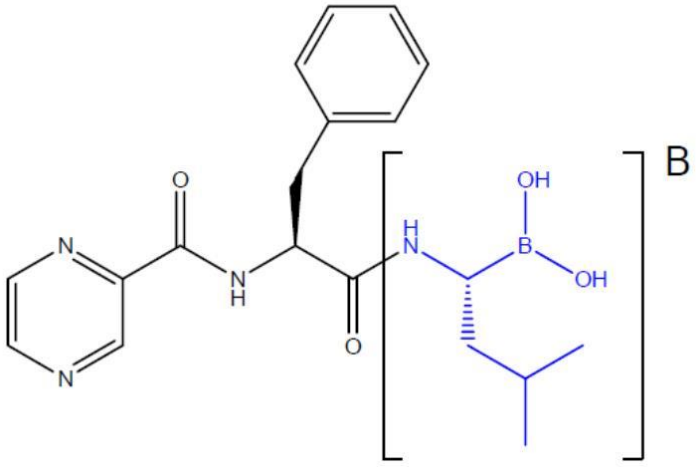


Figure 2

[20] The side chain of P1 is based on leucine (sometimes abbreviated as Leu). It is shown as the three-armed star attached to the dashed line. Therefore, Figure 2 highlights a boroleucine amino acid analog.

[21] The dashed line shows the stereochemistry of the amino acid analog. Most amino acids are chiral, meaning that they can exist in one of two forms that contain the same atoms but are mirror images of each other (enantiomers). These two forms are sometimes referred to as the D and L isomers. A dashed line indicates that the side chain is oriented going into the page. On the other hand, a wedge (as highlighted in Figure 3 below, for example) indicates a side chain that is coming out of the page.

[22] The foregoing explanation of Figure 2 accounts for the "L-leucine boronic acid" portion of the chemical name of bortezomib.

[23] The amino acid highlighted below in Figure 3 is at the P2 position. It is the L enantiomer of phenylalanine (sometimes abbreviated as Phe).

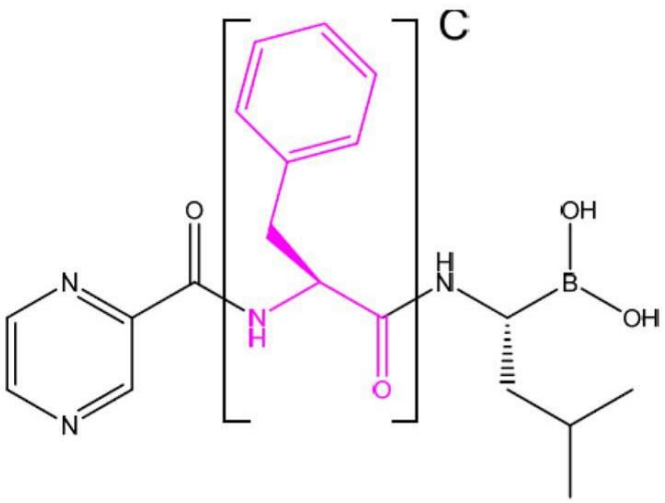


Figure 3

[24] The remainder of the molecule, which is highlighted in Figure 4 below, is pyrazine carbonyl, acting as the N-terminal protecting group.

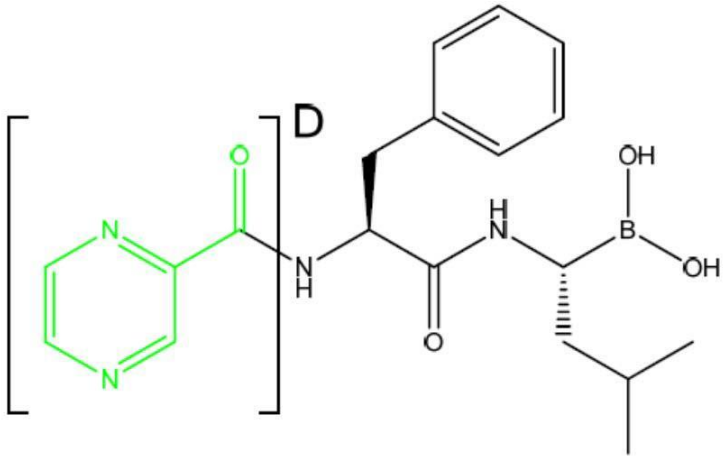


Figure 4

[25] This highlighted portion accounts for the "N-(2-pyrazine)carbonyl" portion of bortezomib's chemical name. The "2" in "2-pyrazine" indicates the position of the nitrogen atoms (shown as N in the molecule) in the pyrazine ring.

[26] There are two different but related uses for an N-terminal protecting group. It may be used during synthesis of a peptide to prevent the N-terminus from reacting in an unwanted way. This type of protecting group is often selected for easy removal in a subsequent step in peptide synthesis when something is to be added at the N-terminus. The second type of N-terminal protecting group is not intended to be removed. It is used when synthesis is complete to stabilize the peptide and assist with binding to the protease. This type is often called a blocking group. In this decision, the terms "protecting group" and "blocking group" are used interchangeably.

[27] There are five characteristic components of the bortezomib molecule that are important to bear in mind:

1. It is a dipeptide;

2. It has a boronic acid warhead;
3. It has a Leu side chain at P1;
4. It has Phe at P2; and
5. It has pyrazine carbonyl as its N-terminal protecting group.

[28] Tripeptides generally offer greater potency than dipeptides, but they are generally more difficult to synthesize, less soluble and less metabolically stable. Tripeptides, being larger molecules than dipeptides, are also more inclined to experience difficulty in penetrating a target cell in order to reach the proteasome. Without cell penetration, even the most potent compound will not be able to inhibit the proteasome *in vivo*. Peptides are synthesized piece by piece. Accordingly, a tripeptide is made from a dipeptide.

III. Overview of the Patents in Suit

[29] Before launching into an analysis of the issues in dispute, it will be useful to provide an overview of each of the patents in suit.

A. *The 936 Patent*

[30] The 936 Patent is entitled "Boronic Ester and Acid Compounds, Synthesis and Uses". It issued to Millennium on April 12, 2005, based on an application that was filed on October 27, 1995 and published on May 9, 1996. The 936 Patent claims priority from US applications that were filed on October 28, 1994 and May 16, 1995, though Millennium does not rely on the first priority application. Accordingly, the parties agree that the claim date of the 936 Patent (explained below) is May 16, 1995. The 936 Patent expired on October 27, 2015, the 20th anniversary of its filing date.

[31] The 936 Patent names six inventors, of whom three testified at trial: Julian Adams, Ross Stein and Louis Plamondon.

[32] The 936 Patent was developed within a small biotech start-up company then known as MyoGenics. MyoGenics was later renamed ProScript. In 1999, ProScript was purchased by Leukocyte. Later that same year, Leukocyte was acquired by Millennium.

[33] Ross Stein was hired at MyoGenics upon its founding in late 1993 as its first scientist. His goal was to find proteasome inhibitors for use in treating muscle wasting associated with cancer. Upon his arrival at MyoGenics, Dr. Stein was aware of the commercial availability of peptide analogs with an aldehyde warhead as proteasome inhibitors. These known aldehyde peptide analogs had potency against the proteasome, but were not sufficiently selective – they had too much potency against non-target proteases. Within a week of his arrival, Dr. Stein decided to explore other warheads using backbones known for aldehydes. These other warheads included boronic acids and various ketones. Dr. Plamondon indicated in his testimony that using known backbones as a starting point is very common in discovery chemistry.

[34] Until the arrival of Julian Adams around March 1994, MyoGenics did not have the expertise to synthesize boronic acid peptide analogs. Even with his arrival, MyoGenics did not have the necessary equipment, and was obliged to go outside to obtain such analogs.

[35] Though results of tests involving ketones were disappointing, the first test with a boronic acid warhead yielded potency 100-times better than the corresponding aldehyde warhead, and with much improved selectivity. This result was particularly encouraging because the comparator

aldehyde compound was one of the best then known. This first test with a boronic acid warhead was with a tripeptide analog. However, the potency was so good that it was decided there was potency to spare and that dipeptide boronic acid analogs should be tested. Results on these further tests were also very encouraging.

[36] Over the following months, Dr. Adams and his colleagues (Dr. Plamondon joined in October 1994) conducted *in vitro* tests on 150 to 200 compounds. About 100 of these tests are reported in the 936 Patent. Table II therein reports K_i values against the proteasome for 93 boronate compounds (boronic acids and esters), seven of which are esters and 86 of which are boronic acids. Of the 93 compounds listed in Table II, five are tripeptides and 88 are dipeptides. All but four of the compounds listed in Table II had L-Leu side chains at P1, like bortezomib. Other side chains tested at P1 were D-Leu and L-Phe. A variety of amino acids were tested at P2. A variety of N-terminal blocking groups were also tested. All of the compounds listed in Table II showed some level of potency.

[37] Tables IV and V in the 936 Patent report on the selectivity of certain of the tested compounds for the proteasome over other proteases. These other proteases are Cathepsin B in Table IV, and Human Leukocyte Elastase, Cathepsin G and Human Pancreatic Chymotrypsin in Table V. All of the boronate compounds listed, five in Table IV and five in Table V, showed selectivity.

[38] Table VI in the 936 Patent reports the results of proteasome inhibition testing inside target cells (IC_{50}) by certain of the compounds listed in Table II. Of the 47 compounds listed in

Table VI, one is an ester and 46 are boronic acids. Also, four are tripeptides and 43 are dipeptides. All of the compounds listed in Table VI showed some level of potency in cells.

[39] Finally, Table VII reports results of testing *in vivo*, in mice. Three compounds were tested in this way, all dipeptide boronic acids. All showed inhibition.

[40] The 936 Patent recognizes that peptidyl boronic acids and esters were known, and had been shown to be inhibitors of certain proteolytic enzymes (proteases) and to inhibit the growth of cancer cells. In this context, the 936 Patent cites the following prior art references: (i) US Patent No. 4,499,082 (the 082 Patent), (ii) US Patent No. 4,537,773, (iii) PCT Application Publication No. WO 91/13904 (the 904 Application), (iv) Kettner et al, "Inhibition of the Serine Proteases Leukocyte Elastase, Pancreatic Elastase, Cathepsin G, and Chymotrypsin by Peptide Boronic Acids" (1984) 259:24 J Biol Chem 15106-15114, and (v) US Patent No. 5,106,948 (the 948 Patent).

[41] Though the 936 Patent describes a broad range of boronic ester and acid compounds, many of which are encompassed within some of the claims thereof, the only claims in issue are 37 and 69. Claim 69 is limited to bortezomib. Claim 37 encompasses bortezomib and five other dipeptidyl boronic acid compounds, all having a Leu side chain at P1.

[42] Generally speaking, the 936 Patent can also be considered the "compound patent".

B. *The 146 Patent*

[43] The 146 Patent is entitled “Formulation of Boronic Acid Compounds”. It issued to the United States of America (as assignee) on March 29, 2011, based on an application that was filed on January 25, 2002 and published on August 1, 2002. Millennium is a licensee of the 146 Patent. The 146 Patent claims priority from a US provisional application that was filed on January 25, 2001. This is therefore the claim date of the 146 Patent. The 146 Patent is set to expire on January 25, 2022, the 20th anniversary of its filing date.

[44] The 146 Patent names a single inventor, Shanker Gupta. However, two co-inventors were added in 2013 by Order of this Court: Valentino J. Stella and Wanda Waugh (*Janssen Inc v Teva Canada Limited* (22 May 2013), Ottawa T-2195-12 (FC)). Dr. Stella testified at the trial before me.

[45] With reference to several prior art references, including US Patent No. 5,780,454 (the 454 Patent) which corresponds to the 936 Patent, the 146 Patent notes that peptide boronic ester and acid compounds are useful as proteasome inhibitors. However, the 146 Patent also notes that certain boronic acid compounds are unstable under certain conditions, thus complicating the characterization of their pharmaceutical agents and limiting their shelf life. The 146 Patent therefore recognizes a need for improved formulations of boronic acid compounds.

[46] Dr. Stella testified that in early 1997 he received from Dr. Gupta the assignment to study bortezomib and create a stable formulation for its administration. He was given the structure of the bortezomib molecule in February 1997 and he received the compound itself in March 1997. In addition to the known instability of bortezomib, Dr. Stella learned quickly that it is difficult to

dissolve. After determining that the solubility of bortezomib was well short of target, Dr. Stella tried various techniques to try to improve the results. None of these efforts was successful in improving solubility without causing other problems.

[47] For reasons that were not clear, Dr. Stella failed to have any literature search conducted concerning bortezomib at the beginning of his research. A literature search was conducted only in August 1997. It is also notable that this initial search failed to reveal the 936 Patent, even though it had been published by then. As a result, Dr. Stella and his team were unaware, during his formulation work, of any of the prior art cited in the 146 Patent. Dr. Stella and his team were also unaware that bortezomib has a tendency to form boroxines, compounds comprising three bortezomib molecules.

[48] Relatively early in his work (in July 1997), Dr. Stella thought to try lyophilisation (freeze-drying) which was known to assist with instability issues generally. Dr. Gupta was opposed to this approach. Dr. Stella had insufficient supplies of bortezomib to test lyophilisation at the same time as other avenues that had Dr. Gupta's support. It was only in October 1997, after other efforts had proved fruitless, that Dr. Gupta reluctantly agreed to tests involving lyophilisation.

[49] As part of their study of bortezomib, Dr. Stella and his team conducted a detailed study of its degradation pathways. This study was published as Wu, Waugh & Stella, "Degradation Pathways of a Peptide Boronic Acid Derivative, 2-Pyz-(CO)-Phe-Leu-$B(OH)_2$" (2000) 89:6 J Pharm Sci at 798-765 (Wu 2000). Wu 2000 disclosed that bortezomib presented erratic stability behaviour. Wu 2000 stated that the degradation of bortezomib is quite complicated, but

concluded that the major degradation pathway is oxidative in nature. Wu 2000 was published early enough to qualify as prior art to the 146 Patent.

[50] The solution offered by the 146 Patent is esters of boronic acids. The claims of the 146 Patent define ester compounds of dipeptide, tripeptide and tetrapeptide boronic acids (claims 1-15, 54, 56), such ester compounds lyophilized (claims 16-32, 55 and 57), methods for preparing such lyophilized compounds (claims 33-53, 58), methods for reconstituting such lyophilized compounds (claims 59-80), and compositions and lyophilized cakes comprising the claimed compounds (claims 81-84).

[51] The claims in issue are claims 30, 45, 46 and 81-84. Claim 30 is simply lyophilized mannitol ester of bortezomib. Claims 45 and 46 both relate to a method of preparing lyophilized mannitol ester of bortezomib as defined in claim 33. Claim 81 is a composition comprising (i) any of the compounds, lyophilized or not, defined in claims 1-32 and 54-57 and (ii) a pharmaceutically-acceptable carrier. Claim 82 is a composition comprising (i) a lyophilized compound prepared in accordance with the method of any one of claims 33-53 and (ii) a pharmaceutically-acceptable carrier. Claim 83 is a lyophilized cake comprising any of the compounds defined in claims 1-32 and 54-57. Claim 84 is a lyophilized cake comprising the compound of formula (1) prepared in accordance with the method of any one of claims 33-53.

[52] Though all of the claims in issue concern lyophilized compounds, many of the compounds contemplated in other claims of the 146 Patent are not defined as being lyophilized.

[53] Just as the 936 Patent can be considered the “compound patent”, the 146 Patent can be considered the “formulation patent”.

C. *The 706 Patent*

[54] The 706 Patent is entitled “Synthesis of Boronic Ester and Acid Compounds”. It issued to Millennium on October 14, 2014, based on an application that is deemed to have been filed on March 24, 2005 and published on October 20, 2005. The 706 Patent is a divisional of Canadian Patent Application No. 2,560,886. The 706 Patent claims priority from a US application that was filed on March 30, 2004. This is therefore the claim date of the 706 Patent. The 706 Patent is set to expire on March 24, 2025, the 20th anniversary of its deemed filing date.

[55] The 706 Patent names seven inventors. One of them, John Bishop, testified at trial.

[56] The 706 Patent concerns the synthesis of boronic ester and acid compounds on a large scale. As in the 146 Patent, the 706 Patent makes reference to several prior art references, including the 454 Patent (which corresponds to the 936 Patent) to state that peptide boronic ester and acid compounds are useful as proteasome inhibitors. The 706 Patent also notes prior art that recognizes bortezomib as one such peptide boronic acid proteasome inhibitor that has shown significant antitumor activity. The 706 Patent indicates that known methods of synthesizing boronic ester and acid compounds were difficult to perform successfully on a production scale.

[57] Dr. Bishop testified that he was hired by Millennium in July 2000 to lead process development for Velcade. Because Phase I tests were showing remarkably good results, there was pressure to accelerate the development of a process for large-scale manufacture of Velcade.

Millennium wanted to achieve in 18 to 24 months what usually takes four to eight years. Simultaneously, Millennium needed product to continue clinical trials. Millennium directed significant resources to Dr. Bishop's group in order to meet these goals.

[58] One early challenge for Dr. Bishop and his team surrounded the fact that bortezomib is very potent and hence highly toxic in production quantities. Special manufacturing facilities were required to address the dangers associated with bortezomib production at large scale. However, peptide synthesis is specialized. Only a limited number of manufacturers were capable of meeting stringent targets for product purity. The usual peptide manufacturers to which Millennium might turn did not have the required special manufacturing facilities to handle bortezomib in large quantities.

[59] Dr. Bishop solved this early challenge by splitting the work. He retained Ash Stevens (who had manufactured early batches for clinical testing) to produce more batches in the short term to permit continued clinical testing. In parallel, he worked with Boehringer Ingelheim (BI) to develop a large-scale production process.

[60] The principal goals of the production process development work were to realize a reliable and commercially feasible large-scale process that would offer purity greater than 99%.

[61] The 706 Patent describes and claims a four-step process for the large-scale manufacture of bortezomib or a boronic acid anhydride thereof, in which each step comprises several sub-steps. These steps and sub-steps are discussed in greater detail in the analysis below of claim

construction for the 706 Patent. The 706 Patent comprises five claims, of which claim 1 is the only independent claim. All five claims are in issue.

[62] The 706 Patent can also be considered the "process patent".

IV. Legal Principles

A. *Claim Construction*

[63] Claims construction is antecedent to consideration of both validity and infringement issues: *Whirlpool Corp v Camco Inc*, 2000 SCC 67 at para 43 [*Whirlpool*]. The same claim construction applies for all issues, including infringement and validity issues: *Whirlpool* at para 49(b).

[64] A patent is not addressed to an ordinary member of the public, but to a worker skilled in the art described as:

> a hypothetical person possessing the ordinary skill and knowledge of the particular art to which the invention relates, and a mind willing to understand a specification that is addressed to him. This hypothetical person has sometimes been equated with the "reasonable man" used as a standard in negligence cases. He is assumed to be a man who is going to try to achieve success and not one who is looking for difficulties or seeking failure.

(See *Free World Trust v Électro Santé Inc*, 2000 SCC 66 at para 44 [*Free World Trust*], quoting from Harold G. Fox, *The Canadian Law and Practice Relating to Letters Patent for Inventions*, 4th ed (Toronto: Carswell, 1969) at 184 [Fox].)

[65] The skilled person to whom the patent is addressed is deemed to be unimaginative and uninventive, but at the same time is understood to have an ordinary level of competence and knowledge incidental to the field to which the patent relates and to be reasonably diligent in keeping up with advances: *AstraZeneca Canada Inc v Apotex Inc*, 2014 FC 638 at para 51, aff'd 2015 FCA 158, rev'd on other grounds 2017 SCC 36.

[66] The person skilled in the art may also be a team of people: *Pfizer Canada Inc v Pharmascience Inc*, 2013 FC 120 at para 28; *General Tire & Rubber Company v Firestone Tyre and Rubber Company Limited*, [1972] RPC 457 at 482 (UKCA).

[67] As stated in *Catnic Components Ltd v Hill & Smith Ltd*, [1982] RPC 183 at 242-243 (UKHL), and quoted in *Whirlpool* at para 44:

> A patent specification should be given a purposive construction rather than a purely literal one derived from applying to it the kind of meticulous verbal analysis in which lawyers are too often tempted by their training to indulge. The question in each case is: whether persons with practical knowledge and experience of the kind of work in which the invention was intended to be used, would understand that strict compliance with a particular descriptive word or phrase appearing in a claim was intended by the patentee to be an essential requirement of the invention so that *any* variant would fall outside the monopoly claimed, even though it could have no material effect upon the way the invention worked.
>
> [Emphasis in original.]

[68] In construing the claims purposively, it is important to bear in mind that the language of the claims is prime: *Free World Trust* at para 40.

[69] The claims language will, on a purposive construction, show that some elements of the claimed invention are essential while others are non-essential. Identification of elements as essential or non-essential is made:

> (i) on the basis of the common knowledge of the worker skilled in the art to which the patent relates;
>
> (ii) as of the date the patent is published;
>
> (iii) having regard to whether or not it was obvious to the skilled reader at the time the patent was published that a variant of a particular element would *not* make a difference to the way in which the invention works; or
>
> (iv) according to the intent of the inventor, expressed or inferred from the claims, that a particular element is essential irrespective of its practical effect;
>
> (v) without, however, resort to extrinsic evidence of the inventor's intention.
>
> [Emphasis in original.]

(See *Free World Trust* at para 31.)

[70] Claim elements are presumed to be essential, and a party alleging otherwise bears the onus of establishing non-essentiality. The Supreme Court of Canada (SCC) in *Free World Trust* at para 55 stated:

> …For an element to be considered non-essential and thus substitutable, it must be shown either (i) that on a purposive construction of the words of the claim it was clearly *not* intended to be essential, or (ii) that at the date of publication of the patent, the skilled addressees would have appreciated that a particular element could be substituted without affecting the working of the invention, i.e., had the skilled worker at that time been told of both the element specified in the claim and the variant and "asked whether the variant would obviously work in the same way", the answer would be yes: *Improver Corp. v. Remington*, [[1990] F.S.R.

> 181], at p. 192. In this context, I think "work in the same way" should be taken for our purposes as meaning that the variant (or component) would perform substantially the same function in substantially the same way to obtain substantially the same result. In *Improver Corp. v. Remington*, Hoffmann J. attempted to reduce the essence of the *Catnic* analysis to a series of concise questions, at p. 182:
>
> > (i) Does the variant have a material effect upon the way the invention works? If yes, the variant is outside the claim. If no: –
> >
> > (ii) Would this (i.e.: that the variant had no material effect) have been obvious at the date of publication of the patent to a reader skilled in the art? If no, the variant is outside the claim. If yes: –
> >
> > (iii) Would the reader skilled in the art nevertheless have understood from the language of the claim that the patentee intended that strict compliance with the primary meaning was an essential requirement of the invention? If yes, the variant is outside the claim.
>
> [Emphasis in original.]

[71] The foregoing questions are sometimes referred to as the *Improver* questions. It is understood that a party seeking to establish that a claim element is not essential (*i.e.*, that the variant falls within the scope of the claim) must be successful on all three questions. Even though the SCC's own phrasing of two questions at the beginning of the passage quoted in the previous paragraph appears to be disjunctive, it seems clear that both questions must be answered in favour of the patentee: *Shire Canada Inc v Apotex Inc*, 2016 FC 382 at paras 137-138.

[72] In construing the claims of a patent, recourse to the disclosure portion of the specification is (i) permissible to assist in understanding the terms used in the claims, (ii) unnecessary where the words are plain and unambiguous, and (iii) improper to vary the scope or ambit of the claims:

Mylan Pharmaceuticals ULC v Eli Lilly Canada Inc, 2016 FCA 119 at para 39 [*Mylan*]; *Procter & Gamble Co v Beecham Canada Ltd* (1982), 61 CPR (2d) 1 at 11, [1982] FCJ No 10 (QL) (FCA).

[73] Terms used in the claims must be read in the context of the patent as a whole, and it is therefore unsafe in many instances to conclude that a term is plain and unambiguous without a careful review of the specification: *Whirlpool* at para 52, quoting from William L. Hayhurst, "The Art of Claiming and Reading a Claim" in Gordon F. Henderson, ed, *Patent Law of Canada* (Toronto: Carswell, 1994) 190.

[74] Because there is potential for tension between the guidance provided in the preceding two paragraphs, I reproduce here the discussion of Justice Russell Zinn in *Janssen-Ortho Inc v Canada (Health)*, 2010 FC 42 at paras 115-116, 119, on this point, with which I agree:

> [115] In my view, the whole of the specification (including the disclosure and the claims) may be examined to ascertain the nature of the invention. Where the words of the claims are plain and unambiguous and capable of only one interpretation by a person skilled in the art, recourse to the disclosure is unnecessary. This is not to say that the interpreter should not examine the disclosure. In my view, one should do so, but with caution. Recourse may be had to the disclosure for the purpose of confirming the interpretation arrived at from examining the claims alone or to disclose an ambiguity in the language of the claims that was not otherwise evident. However, the patentee cannot expand the monopoly specifically expressed in the claims by borrowing phrases from the disclosure and placing them into the language of the claims.
>
> [116] I agree with Novopharm that when one looks beyond the language of the claims at issue one ought first look at the dependent claims as an aid to interpreting the independent claims, before one resorts to the disclosure.
>
> […]

> [119] I do not take the Supreme Court of Canada to be saying that in every case one must examine the disclosure prior to construing the claims of the patent; rather, I take the Court in *Whirlpool* and *Free World Trust* to be raising a caution that one should not reach a firm conclusion as to the meaning of the words in the claims being construed without having tested one's initial interpretation against the words of the disclosure. When that is done, if the disclosure suggests another interpretation of the terms used in the claims, then resort to the meanings given in the disclosure is proper, subject to the proviso that the invention that is protected is what is expressed in the claims which cannot be added to by anything mentioned in the disclosure that has not found its way into the claims as drafted. As was noted by Justice Taschereau in Metalliflex Ltd. v. Rodi & Wienenberger Aktiengesellschaft, [1961] S.C.R. 117, at p. 122:
>
> > The claims, of course, must be construed with reference to the entire specifications, and the latter may therefore be considered in order to assist in apprehending and construing a claim, but the patentee may not be allowed to expand his monopoly specifically expressed in the claims "by borrowing this or that gloss from other parts of the specifications".
>
> [All emphasis by Zinn J.]

[75] As stated in *Consolboard Inc v MacMillan Bloedel (Sask) Ltd*, [1981] 1 SCR 504 at 520:

> We must look to the whole of the disclosure and the claims to ascertain the nature of the invention and methods of its performance, (*Noranda Mines Limited v. Minerals Separation North American Corporation* [[1950] S.C.R. 36]), being neither benevolent nor harsh, but rather seeking a construction which is reasonable and fair to both patentee and public. There is no occasion for being too astute or technical in the matter of objections to either title or specification for, as Duff C.J.C. said, giving the judgment of the Court in *Western Electric Company, Incorporated, and Northern Electric Company v. Baldwin International Radio of Canada* [[1934] S.C.R. 570], at p. 574, "where the language of the specification, upon a reasonable view of it, can be so read as to afford the inventor protection for that which he has actually in good faith invented, the court, as a rule, will endeavour to give effect to that construction". Sir George Jessel spoke to like effect at a much earlier date in *Hinks & Son v.*

> *Safety Lighting Company* [(1876), 4 Ch. D. 607]. He said the patent should be approached "with a judicial anxiety to support a really useful invention".

[76] If a patentee has put something in the patent specification that plainly tells the reader that, for the purpose of the specification, s/he is using a particular word with a meaning which s/he sets out, then the reader knows that when s/he comes to the claims, s/he must read that word as having that meaning: *Lundbeck Canada Inc v Ratiopharm Inc*, 2009 FC 1102 at para 46; *Minerals Separation North American Corp v Noranda Mines Ltd* (1952), , 15 CPR 133, 69 RPC 81, [1952] JCJ No 2 (QL) (UKPC) at para 17. The specification is the inventor's lexicon: *SNF Inc v Ciba Specialty Chemicals Water Treatments Ltd*, 2015 FC 997 at para 129, aff'd 2017 FCA 225.

[77] The words chosen by the inventor will be read in the sense the inventor is presumed to have intended, and in a way that is sympathetic to accomplishment of the inventor's purpose expressed or implicit in the text of the claims. However, if the inventor has misspoken or otherwise created an unnecessary or troublesome limitation in the claims, it is a self-inflicted wound. The public is entitled to rely on the words used, provided the words used are interpreted fairly and knowledgeably: *Free World Trust* at para 51.

B. *Obviousness*

[78] Once it has issued, a patent benefits from a rebuttable presumption that it is valid: s. 43(2) of the *Patent Act*, RSC 1985, c P-4. Accordingly, Teva bears the burden of proving its allegations of obviousness.

[79] The issue of obviousness begins with s. 28.3 of the *Patent Act*:

Invention must not be obvious	**Objet non évident**
28.3 The subject-matter defined by a claim in an application for a patent in Canada must be subject-matter that would not have been obvious on the claim date to a person skilled in the art or science to which it pertains, having regard to	**28.3** L'objet que définit la revendication d'une demande de brevet ne doit pas, à la date de la revendication, être évident pour une personne versée dans l'art ou la science dont relève l'objet, eu égard à toute communication :
(a) information disclosed more than one year before the filing date by the applicant, or by a person who obtained knowledge, directly or indirectly, from the applicant in such a manner that the information became available to the public in Canada or elsewhere; and	a) qui a été faite, plus d'un an avant la date de dépôt de la demande, par le demandeur ou un tiers ayant obtenu de lui l'information à cet égard de façon directe ou autrement, de manière telle qu'elle est devenue accessible au public au Canada ou ailleurs;
(b) information disclosed before the claim date by a person not mentioned in paragraph (a) in such a manner that the information became available to the public in Canada or elsewhere.	b) qui a été faite par toute autre personne avant la date de la revendication de manière telle qu'elle est devenue accessible au public au Canada ou ailleurs.

[80] Pursuant to s. 28.3(b), a patent claim will be invalid if, based on information that was available to the public before the claim date, its subject-matter would have been obvious to a person skilled in the art or science to which it pertains.

[81] The threshold for inventiveness (non-obviousness) has long been understood to be low. As stated in *Beloit Canada Ltd v Valmet Oy* (1986), 8 CPR (3d) 289, [1986] FCJ No 87 (QL) at 294-295 (FCA):

> The test for obviousness is not to ask what competent inventors did or would have done to solve the problem. Inventors are by definition inventive. The classical touchstone for obviousness is the technician skilled in the art but having no scintilla of inventiveness or imagination; a paragon of deduction and dexterity, wholly devoid of intuition; a triumph of the left hemisphere over the right. The question to be asked is whether this mythical creature (the man in the Clapham omnibus of patent law) would, in the light of the state of the art and of common general knowledge as at the claimed date of invention, have come directly and without difficulty to the solution taught by the patent. It is a very difficult test to satisfy.
>
> …
>
> Every invention is obvious after it has been made, and to no one more so than an expert in the field. Where the expert has been hired for the purpose of testifying, his infallible hindsight is even more suspect. It is so easy, once the teaching of a patent is known, to say, "I could have done that"; before the assertion can be given any weight, one must have a satisfactory answer to the question, "Why didn't you?"

[82] Obviousness was discussed by the SCC in *Apotex Inc v Sanofi-Synthelabo Canada Inc*, 2008 SCC 61 [*Sanofi*]. At para 67 of that decision, the Court borrowed the following approach to assessing obviousness from *Pozzoli SPA v BDMO SA,* [2007] FSR 37 (p 872), [2007] EWCA Civ 588 (UKCA) at para 23:

> (1) (a) Identify the notional "person skilled in the art";
>
> (b) Identify the relevant common general knowledge of that person;
>
> (2) Identify the inventive concept of the claim in question or if that cannot readily be done, construe it;

> (3) Identify what, if any, differences exist between the matter cited as forming part of the "state of the art" and the inventive concept of the claim or the claim as construed;
>
> (4) Viewed without any knowledge of the alleged invention as claimed, do those differences constitute steps which would have been obvious to the person skilled in the art or do they require any degree of invention?

[83] The SCC then noted that the fourth step in this approach may give rise to the issue of whether the invention was "obvious to try". The Court indicated that the "obvious to try" test might be appropriate in areas of endeavour where advances are often won by experimentation, where there may be numerous interrelated variables with which to experiment. The parties do not dispute that the "obvious to try" test is appropriate in the present case. However, a finding that an invention was "obvious to try" requires evidence to convince a judge on a balance of probabilities that it was more or less self-evident to try to obtain the invention. Mere possibility that something might turn up is not enough: *Sanofi* at para 66.

[84] At para 69 of its decision, the SCC provided the following non-exhaustive list of factors applicable in assessing obviousness to try:

> 1. Is it more or less self-evident that what is being tried ought to work? Are there a finite number of identified predictable solutions known to persons skilled in the art?
>
> 2. What is the extent, nature and amount of effort required to achieve the invention? Are routine trials carried out or is the experimentation prolonged and arduous, such that the trials would not be considered routine?
>
> 3. Is there a motive provided in the prior art to find the solution the patent addresses?

[85] The SCC also referred to the actual course of conduct which culminated in the making of the invention as another important factor may arise. However, this can be considered as part of the second factor in the previous paragraph.

[86] The test of obviousness is not to be applied to each element of invention discretely but rather to the combination of elements as a whole: *Procter & Gamble Pharmaceuticals Canada Inc v Canada (Minister of Health)*, 2004 FC 204 at para 95, aff'd 2004 FCA 393, leave to appeal to SCC refused.

(1) Selection Patents

[87] For reasons that are discussed later in analysis of the 936 Patent, it is necessary to consider the law concerning selection patents.

[88] The SCC provided the following discussion of selection patents in *Sanofi* at para 9:

> The *locus classicus* describing selection patents is the decision of Maugham J. in *In re I. G. Farbenindustrie A. G.'s Patents* (1930), 47 R.P.C. 289 (Ch. D.). At p. 321, he explained that in the field of chemical patents (which would of course include pharmaceutical compounds), there are often two "sharply divided classes". The first class of patents, which he called originating patents, are based on an originating invention, namely, the discovery of a new reaction or a new compound. The second class comprises patents based on a selection of compounds from those described in general terms and claimed in the originating patent. Maugham J. cautioned that the selected compounds cannot have been made before, or the selection patent "would fail for want of novelty". But if the selected compound is "novel" and "possess[es] a special property of an unexpected character", the required "inventive" step would be satisfied (p. 321). At p. 322, Maugham J. stated that a selection patent "does not in its nature differ from any other patent".

[89] In *Sanofi* at para 10, the SCC provided the following non-exhaustive list of conditions that must be satisfied for a selection patent to be valid:

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

[90] An invalid selection is not an independent ground of invalidity. Rather, the conditions for a valid selection patent serve to characterize the patent and accordingly inform the obviousness analysis: *Eli Lilly Canada Inc v Novopharm Limited*, 2010 FCA 197 at para 27.

(2) Commercial Success/Meritorious Awards

[91] Commercial success and meritorious awards are two secondary factors that may be relevant to the assessment of obviousness: *Novopharm Limited v Janssen-Ortho Inc*, 2007 FCA 217 at para 25. However, these factors are not conclusive. Commercial success cannot save an invention that is obvious: *Domtar Ltd v MacMillan Bloedel Packaging Ltd* (1978), 41 CPR (2d) 182, [1978] FCJ No 906 (QL) (FCA). Commercial success is relevant only in borderline cases: *Rothmans, Benson & Hedges Inc v Imperial Tobacco Ltd* (1993), 47 CPR (3d) 188, [1993] FCJ No 135 (QL) (FCA), quoting from Fox.

[92] There must be a causal relationship between the alleged invention and any commercial success: D.H. MacOdrum, *Fox on the Canadian Law of Patents*, 5th ed (Toronto, Ont: Thomson Reuters Canada, 2013), ch 4:18 at 4-158.1; *Corning Glass Works v Canada Wire & Cable Ltd* (1984), 81 CPR (2d) 39, [1984] FCJ No 353 (QL) (FCA); *Pollard Banknote Limited v BABN Technologies Corp*, 2016 FC 883 at para 224. It may be that commercial success is due to other factors. The same may be said of meritorious awards.

[93] In the present case, there is an added complexity because of the involvement of three different patents. There is little doubt that Millennium's Velcade product has experienced tremendous commercial success both in Canada and around the world. There is also evidence of many awards and accolades associated with the success of Velcade. But it also appears that such success required the inventions of all three patents in suit. No single one of these patents could have given rise to the commercial success. Millennium's argument on this issue cites the fact that each vial of the Velcade product contains the embodiment of all three patents.

[94] The parties have not cited any jurisprudence in which a series of patents were necessary to commercial success. In my view, I must consider the issue of commercial success separately for each patent, just as I must consider the broader issue of obviousness separately for each patent.

C. *Infringement*

[95] Infringement is not defined in the *Patent Act*. The exclusive rights associated with a patent are set out in s. 42 of the *Patent Act*:

Grant of Patents	**Octroi des brevets**
Contents of patent	**Contenu du brevet**
42 Every patent granted under this Act shall contain the title or name of the invention, with a reference to the specification, and shall, subject to this Act, grant to the patentee and the patentee's legal representatives for the term of the patent, from the granting of the patent, the exclusive right, privilege and liberty of making, constructing and using the invention and selling it to others to be used, subject to adjudication in respect thereof before any court of competent jurisdiction. [Emphasis added.]	**42** Tout brevet accordé en vertu de la présente loi contient le titre ou le nom de l'invention avec renvoi au mémoire descriptif et accorde, sous réserve des autres dispositions de la présente loi, au breveté et à ses représentants légaux, pour la durée du brevet à compter de la date où il a été accordé, le droit, la faculté et le privilège exclusif de fabriquer, construire, exploiter et vendre à d'autres, pour qu'ils l'exploitent, l'objet de l'invention, sauf jugement en l'espèce par un tribunal compétent. [Je souligne.]

[96] Once the claims of a patent have been properly construed by determining the essential elements thereof, the issue of whether a product infringes the patent is simply a matter of determining whether all of the essential elements of the claims in question are present. There is no infringement if an essential element is different or omitted. There may still be infringement, however, if non-essential elements are substituted or omitted: *Free World Trust* at para 31.

V. Witnesses

[97] The Court heard from 15 witnesses during the trial, including seven fact witnesses and four experts on behalf of Millennium, and four experts on behalf of Teva. Teva called no fact witnesses.

[98] The paragraphs below set out, for each witness, a brief statement of their testimony, including some or all of the following: who they are, what they testified about, and my general impressions of their testimony.

A. *Millennium's Fact Witnesses*

(1) Dixie-Lee Esseltine

[99] Dr. Esseltine is a Board-certified medical doctor specialized in internal medicine and hematology. As part of the clinical team responsible for the early development of bortezomib, Dr. Esseltine was responsible for the safety of the patients enrolled in Phase I and Phase II clinical trials and acted as the medicinal monitor. Dr. Esseltine spoke of the breakthrough nature and the success of bortezomib, highlighting the successful clinical trials that led to the approval process being fast-tracked in the US. She discussed the international acclaim, including the Warren Alpert Foundation award which recognized Velcade as a "pioneering cancer drug".

(2) James Brodie

[100] Mr. Brodie is the Vice-President of Marketing at Johnson & Johnson Medical Products, a sister company to the defendant Janssen. He previously worked for Janssen, where he held multiple positions during a span of 20 years, including sales and marketing of various types of drugs. At one time, a significant part of his responsibility was in overseeing the strategy and tactical execution of commercializing Velcade.

[101] Mr. Brodie described NOC approvals and discussed Health Canada's accelerated approval framework. He testified that Janssen saw high double-digit growth in sales from 2005

through 2010, with peak sales reported in 2014, the year before Teva entered the market with its generic version of Velcade.

(3) Julian Adams

[102] Dr. Adams is a named inventor of the 936 Patent. He did PhD studies in chemistry at the Massachusetts Institute of Technology, and a postdoctoral fellowship at Columbia University. He worked on boronic acid inhibitors of peptides (among other things) at BI for a few years before joining MyoGenics around March 1994. There, he spearheaded a change of focus from aldehyde inhibitors of the proteasome to boronic acid inhibitors, which ultimately led to the creation of bortezomib.

[103] Dr. Adams was introduced to the proteasome during the recruitment process at MyoGenics. In cross-examination, he also acknowledged that he attended a presentation during this time at which Ross Stein (another named inventor of the 936 Patent) suggested the use of boronic acids as proteasome inhibitors. Dr. Adams described the process of developing and testing bortezomib, and later efforts to develop a stable formulation thereof.

[104] In respect of the 146 Patent, Dr. Adams suggested that it was not obvious to try lyophilisation when faced with less than satisfactory results from a liquid formulation. However, in a previous examination, he had adopted a statement stating the contrary. Millennium objected to the line of questioning on this point in cross-examination. After hearing some argument, I decided to allow the line of questioning to continue subject to hearing further argument concerning admissibility in closing. Having heard no such argument, I see no reason to exclude this line of questioning.

[105] My impression of Dr. Adams was not entirely positive. He seemed to be disinclined to concede points that might disfavour Millennium. He frequently relied on "I don't recall" as an answer, especially when the answer might favour Teva. He was initially reluctant to acknowledge that the 904 Application discussed inhibition of the proteasome, even though it is noted in the 936 Patent. He later conceded this point. With regard to an admission he had made in a 2011 examination for discovery that one reason for having chosen a dipeptide over a tripeptide was improved cell penetration, he initially stated that he had been referring to penetration of the GI tract, not a target cell wall. Further review of the transcript of his 2011 examination forced him to back off from this position. Finally, I am concerned that, after many years of claiming to be the first to conceive the idea of trying boronic acids as proteasome inhibitors, he acknowledged in cross-examination for the first time that he may actually have gotten the idea from Dr. Stein. The fact that this admission arose now as a result of seeing notes that he had not seen in 20 years does not allay my concern.

[106] I accept Dr. Adams' testimony concerning the major events surrounding the development of Velcade, but I am hesitant to rely on his testimony where it is based on his memory or concerns matters of subjective impression or opinion, especially where it is uncorroborated or inconsistent with past statements he has made.

(4) Louis Plamondon

[107] Dr. Plamondon has a PhD in organic chemistry from the University of Montreal. He did two years of postdoctoral work at Harvard University in organic synthesis, and later joined BI where he worked mainly on HIV protease inhibitors. He joined MyoGenics in October 1994, as a

Senior Scientist reporting to Dr. Adams and working primarily on synthesizing and testing various compounds for proteasome inhibition. He is a named inventor in the 936 Patent.

[108] Dr. Plamondon discussed the testing process that led to the selection of bortezomib as the lead compound. He described it as a complex and very interactive process.

[109] Generally, Dr. Plamondon was credible and seemed to answer questions frankly, though he did seem eager to emphasize the amount of work involved in identifying the drug candidate that was eventually brought to market.

(5) Ross Stein

[110] A named inventor in the 936 Patent, Dr. Stein holds a PhD in organic chemistry and biochemistry from Indiana University, followed by postdoctoral work at Washington University and the University of Kansas. As indicated in paragraph [33] above, he joined MyoGenics upon its founding in late 1993 to develop proteasome inhibitors. At that time, he had 20 years' experience working with proteases, but none with the proteasome.

[111] Dr. Stein discussed a few misconceptions in the literature in relation to the proteasome at that time, including with respect to its catalytic activities. He also stated that his idea for inhibiting the proteasome with boronates came to him within a week of joining MyoGenics, based on his knowledge of the literature.

[112] Dr. Stein seemed completely credible and frank, demonstrating no bias.

(6) Valentino Stella

[113] Dr. Stella obtained a PhD in analytical pharmaceutical chemistry and pharmaceutics, and spent most of his career as a professor at the University of Kansas. His primary area of research was in drug formulation, including Velcade. He is a named inventor of the 146 Patent.

[114] Dr. Stella discussed the process of developing Velcade, including (i) receiving instructions from Shanker Gupta of the National Cancer Institute; (ii) receiving samples of several compounds for testing, including bortezomib; (iii) various preliminary studies he conducted on bortezomib, including with regard to solubility and degradation; (iv) attempts to make a practical liquid formulation; and (v) development efforts using lyophilisation, including options for excipients.

[115] Dr. Stella is very knowledgeable and confident. He answered questions directly. I accept his testimony as reliable.

(7) John Bishop

[116] Dr. Bishop obtained a PhD in organic chemistry from the University of California, Berkley. Thereafter, he completed one year of postdoctoral work at the Lawrence Berkley National Laboratory working on drug discovery, followed by a two-year military obligation working on chemical research. He has spent most of his career to date in industry, most notably at Millennium for four years, including as its Director of Chemical and Biologics Process Development. Dr. Bishop is a named inventor of the 706 Patent.

[117] At trial, Dr. Bishop described the evolution of the manufacturing processes for what became Velcade, including operational efficiency and purity issues relating to the transition from a clinical process to an acceptable commercial scale process. He emphasized that safety was a primary concern and that every experiment was a formidable undertaking.

[118] Dr. Bishop answered questions with great precision, rarely answering yes or no to a direct question in cross-examination. However, I did not detect any attempt to evade questions. I also did not detect any bias in his answers.

B. *Millennium's Expert Witnesses*

(1) Alexander Vinitsky

[119] Dr. Vinitsky received a PhD in biology from New York University and was a Postdoctoral Fellow at Mount Sinai School of Medicine, doing proteasome biochemistry work in the laboratory of Dr. Marian Orlowski, whose group was the first to purify and characterize the proteasome. Two of his articles published as a result of this work at Mount Sinai were cited at trial as prior art. The parties have agreed, and I accept, that Dr. Vinitsky is an expert in proteasome biochemistry and proteasome inhibitor design up to the state of the art in 1996, as well as an expert in enzymology and drug discovery.

[120] Dr. Vinitsky's testimony related to the 936 Patent and was submitted in an expert report that also addressed Dr. Wilk's expert report. Specifically, Dr. Vinitsky opined that the compounds defined in the claims in issue of the 936 Patent are potent and selective inhibitors of

the proteasome which were original and whose characteristic components were not obvious to try.

[121] My general impression is that Dr. Vinitsky did not take to heart all of the requirements of the Code of Conduct for Expert Witnesses that he signed. He seemed reluctant to concede points when it was unfavourable to Millennium (for instance, whether the 904 Application describes the use of boronic acids to inhibit the proteasome). In my view, Dr. Vinitsky thereby showed some bias. He also seemed to apply a different standard to the relevance of certain data depending on whether the point favoured Millennium or Teva (for instance, whether a certain level potency was good or not, whether data based on testing only a single concentration was worthy of consideration, or whether predictions can be made about potency without experimental data). Dr. Vinitsky also distinguished the claimed compounds from those known in the prior art on the basis that none of the prior art compounds had shown the level of potency and selectivity that the claimed compounds do. In cross-examination, he was forced to acknowledge that he could not support that statement for all of the compounds defined in the claims in issue of the 936 Patent since not all such compounds had test results for these properties reported in the 936 Patent. Finally, he occasionally slipped into very technical language that sometimes made his testimony difficult to follow in real time.

[122] Generally speaking, I am hesitant to accept Dr. Vinitsky's opinion when it is inconsistent with that of Dr. Wilk.

(2) Roger Snow

[123] Dr. Snow holds a PhD in chemistry from Cambridge University in England. He conducted postdoctoral research at Columbia University before returning to Cambridge University upon being elected to a Research Fellowship. Dr. Snow joined BI in 1991 as a Principle Scientist working mainly on inhibiting an enzyme called dipeptidyl peptidase 4 (DPP4) using boronic acids. At that time, he reported directly to Dr. Adams. Dr. Snow co-authored a book chapter on boronic acid inhibitors with Teva's expert Dr. Bachovchin. Dr. Snow left BI in 2011 to pursue his career in academia. He currently teaches organic chemistry at Vassar College in Poughkeepsie, New York.

[124] There is a dispute over Dr. Snow's expert qualifications. Millennium asserts that it is as follows: "Dr. Snow has a PhD in Organic Chemistry, and is an expert in medicinal chemistry, synthetic organic chemistry, boronic acid chemistry, and in the use of boronic acid inhibitors to inhibit proteases." Teva disagrees with regard to Dr. Snow's expertise in boronic acid chemistry and in the use of boronic acids as inhibitors of proteases, which Teva argues goes to the weight rather than the admissibility of his testimony. Teva points to the failure of his CV to claim expertise in these areas, but I am satisfied that he has the required expertise to meet Millennium's definition.

[125] Dr. Snow testified in relation to the 936 and 146 Patents, submitting two expert reports. He also addressed Dr. Bachovchin's expert report. He stated that his expertise is as a medicinal chemist, not a formulator.

[126] In his first expert report, Dr. Snow concluded that Teva's bortezomib product contains all of the essential elements of the claims of the 936 Patent. In his second report, Dr. Snow opined that the claims in issue of the 936 and 146 Patents would not have been obvious. With respect to the 936 Patent, he stated that the prior art would not have directed the skilled person to the characteristic components of bortezomib and that these components would not have been obvious to try. On the 146 Patent, Dr. Snow opined that the skilled person would not have been able to predict that formation of a boronate ester, by lyophilizing bortezomib with mannitol, would improve the stability and dissolution rate of bortezomib.

[127] Dr. Snow was much better at explaining himself in understandable terms than Dr. Vinitsky. He also came across as less biased, though I remain concerned with his refusal to give simple answers to simple questions where those answers did not favour Millennium. He also seemed to have set the bar too high for predictability, apparently requiring near certainty.

(3) Bradley Anderson

[128] Dr. Anderson holds a PhD in pharmaceutical chemistry from the University of Kansas. He worked in industry for a few years before returning to academia. He has been involved in drug formulation throughout his career, with an emphasis on anti-cancer and anti-HIV drugs. He is currently a Professor in the Department of Pharmaceutical Sciences at the College of Pharmacy of the University of Kentucky. The parties agree, as do I, that Dr. Anderson is an expert in pharmaceutical formulation, though he acknowledged in cross-examination that he has never worked with boronic acids.

[129] Dr. Anderson submitted two expert reports concerning the 146 Patent and commenting on the expert reports of Teva's experts Drs. Bachovchin and Suryanarayanan. In his first expert report, Dr. Anderson construed the claims of the 146 Patent, concluded that Teva's bortezomib products contain all of the elements thereof, and opined that the skilled person to whom the 146 Patent is directed is a pharmaceutical formulator, who need not have expertise in boron chemistry. In his second expert report, Dr. Anderson stated that the skilled person might consult a medicinal chemist, but did not acknowledge that a medicinal chemist would be part of the team that make up the skilled person. That acknowledgement came only in cross-examination and only reluctantly. In that second expert report, Dr. Anderson also opined that the lyophilized mannitol boronic ester of bortezomib was new and had unexpected properties, and was therefore not obvious. He also asserted that it would not have been predictable that the ester formation would be easily reversible, and so the skilled person would have been dissuaded from trying lyophilisation.

[130] Dr. Anderson showed bias by his reluctance to acknowledge his view that a medicinal chemist would be part of the skilled person team. As with other experts on behalf of Millennium, I am also concerned with Dr. Anderson's reluctance to give simple answers to simple questions when the answer did not favour Millennium. He was repeatedly evasive of direct questions during cross-examination. I found that the more difficult Dr. Anderson's position became, the vaguer his answers became. Dr. Anderson also showed some inconsistency in asserting on the one hand that a formulator does not want to alter the chosen drug compound (when considering ester formation), but on the other hand not seeing the same reserve in the skilled person when considering whether a formulator would consider a solid oral dosage form instead of an injectable solution.

(4) Anthony Barrett

[131] Dr. Barrett obtained a PhD in organic chemistry from Imperial College of Science, Technology and Medicine in London. He lectured at Imperial College for a few years before moving to the United States where he taught organic chemistry at Northwestern University and at Colorado State University before returning to Imperial College. The parties agree that Dr. Barrett is qualified as an expert in chemistry, organic chemistry, synthetic organic chemistry, organic and medicinal compound synthesis, manufacturing processes for pharmaceuticals and fine specialty chemicals, and chemistry research techniques. Millennium also asserts that Dr. Barrett's expertise extends to process scale-up. Teva disputes this aspect of Dr. Barrett's expertise, but the parties agree that this dispute goes to the weight of his testimony and not its admissibility.

[132] Dr. Barrett engaged in a detailed analysis of the disclosure in the 706 Patent to support his views concerning construction of the claims and the non-essentiality of certain elements thereof. He opined that the chemistry of large scale manufacturing differs from that used on a small scale, and that synthetic chemistry is not straightforward.

[133] Dr. Barrett is clearly very knowledgeable in the area of process chemistry and scale-up, and he was eager to speak on the subject. This meant that his answers often strayed from the questions asked. This happened even in direct examination. He was reticent to answer cross-examination questions where the answer did not favour Millennium. As a result, he did not give the impression of being neutral or impartial. He was interested in educating the Court, but only in favour of Millennium. For example, he repeatedly stated that dichlorobenzene was an example of

an alternative solvent for ethyl acetate in the 706 Patent, even though this was not mentioned in his reports. Once or twice would have been adequate to make his point, but more than that betrayed his bias. Dr. Barrett spent far too much time in cross-examination discussing what he wanted to talk about rather than what Teva's counsel was asking about.

C. *Teva's Expert Witnesses*

(1) Raj Suryanarayanan

[134] Dr. Suryanarayanan received his PhD in pharmaceutical sciences from the University of British Columbia. Since then, he has conducted research and taught at the Department of Pharmaceutics at the University of Minnesota in Minneapolis. He has published extensively in the field of lyophilisation, including the behaviour of mannitol in freeze-dried formulations. The parties agree, and I concur, that he has expertise in material science of pharmaceutical solids and pharmaceutical formulations including lyophilized formulations.

[135] Dr. Suryanarayanan submitted two expert reports regarding the 146 Patent. In the first, he opined that the skilled person to whom the 146 Patent is directed is a team comprising a formulation scientist and a medicinal chemist, and that it would have been obvious to this skilled person to lyophilize bortezomib in mannitol. His second expert report responded to Dr. Anderson's expert reports.

[136] Dr. Suryanarayanan answered questions clearly in his testimony in chief and in cross-examination. He did not try to evade questions, and did not appear to attempt to colour his answers to favour Teva. I found Dr. Suryanarayanan to be a reliable witness.

(2) Sherwin Wilk

[137] Dr. Wilk received a PhD in biochemistry from Fordham University. He did postdoctoral studies at Cornell University College of Medicine. His career has been entirely focused on protease biochemistry. Dr. Wilk has been a faculty member at the Department of Pharmacological Sciences at Mount Sinai School of Medicine in New York since 1969. The parties agree, as do I, that Dr. Wilk's expertise may be defined as follows: "Professor Wilk is a biochemist who was co-discoverer of the proteasome. He has expertise in protease and proteasome purification, and in the field of proteolytic enzymes, including the synthesis of peptide analogue inhibitors of the proteasome."

[138] Dr. Wilk submitted two expert reports regarding the 936 Patent. In his first report, he provided a scientific primer on proteasome science and discussed the relevant common general knowledge in 1995 relating to protease inhibitors and related residues. He concluded that it would have been obvious to make a proteasome inhibitor with the characteristic components of bortezomib. His second expert report addressed some of Dr. Vinitsky's opinions.

[139] Dr. Wilk was very knowledgeable and not biased in his answers, which he gave without hesitation or evasion. He readily conceded points during cross-examination, but energetically defended others. I found Dr. Wilk to be a reliable witness.

(3) William Bachovchin

[140] Dr. Bachovchin has a PhD in chemistry from the California Institute of Technology. He did postdoctoral studies there and at Harvard Medical School. His research has focused mostly

on proteases, with a heavy emphasis on designing peptide boronic acid inhibitors as potential drugs. Dr. Bachovchin has been a faculty member at Tufts University School of Medicine since 1979, where he is currently a Professor of Developmental, Molecular, and Chemical Biology. The parties agree, as do I, that Dr. Bachovchin is a "medicinal chemist with expertise in the area of boronic acid chemistry and the design and use of boronic acid peptide analogues as protease inhibitors."

[141] Dr. Bachovchin submitted two expert reports relating to the 936 and 146 Patents. He also addressed the second expert reports of both Dr. Snow and Dr. Anderson. In his first report, Dr. Bachovchin provided a helpful primer on the relevant organic chemistry. He also concluded that the claims in issue of both the 936 and 146 Patents would have been obvious to the skilled person at the respective claim dates. In respect of the 936 Patent, he concluded that each of the characteristic components of bortezomib would have been obvious to try. In respect of the 146 Patent, he stated that lyophilisation was a well-known method of reducing instability that would have been obvious to try in bortezomib. He also stated that the skilled person would have known that a bulking agent would be needed and that mannitol would have been obvious to try. He further stated that the skilled person would have been aware of the possibility that an ester would form, but would not have been dissuaded by this since it would have been expected that such ester formation would be readily reversible.

[142] Dr. Bachovchin was a good witness. His evidence remained largely unchallenged on cross-examination. He was firm in his view, but conceded points readily when appropriate.

(4) George Kabalka

[143] Dr. Kabalka received a PhD from Purdue University in organoborane chemistry (this is the branch of organic chemistry concerning boron). He is Professor Emeritus with the Department of Chemistry at the University of Tennessee in Knoxville where he spent the entirety of his professional career and where he taught organic chemistry almost exclusively. He is also a Professor in the Radiology Department in the Faculty of Medicine. The parties agree that Dr. Kabalka is a chemist with expertise in the field of synthetic organic chemistry, medicinal chemistry, and organoborane chemistry.

[144] Dr. Kabalka testified that chemistry scale-up was not a distinct area of study at the time of the 706 Patent. His position was that all of the claim elements in issue of the 706 Patent are essential, and that there was nothing inventive in the scale-up of the process to synthesize the compound in issue.

[145] Dr. Kabalka's testimony was very helpful. He answered questions directly and honestly. I found him entirely credible. Clearly, his expertise in scaling up is not as extensive as Dr. Barrett's. However, their relative level of expertise is not determinative of the weight to be given to their respective opinions.

VI. Analysis

[146] Before embarking on the analysis of the issues in dispute, it is useful to repeat those issues here:

1. With regard to the 936 Patent:

a. Whether claims 37 and 69 are obvious;

2. With regard to the 146 Patent:

    a. What is the inventive concept, and

    b. Whether the asserted claims are obvious;

3. With regard to the 706 Patent:

    a. How the claims should be construed,

    b. Whether Teva-bortezomib infringes,

    c. Whether Act-bortezomib infringes, and

    d. Whether the asserted claims are obvious.

[147] Because the determination of the inventive concept is part of the assessment of obviousness, I will deal with the 146 Patent as a single issue.

A. *936 Patent: Obviousness*

[148] Teva's allegations that claims 37 and 69 of the 936 Patent are obvious depend on an argument that bortezomib falls within the scope of several prior art references, principally the 904 Application. Teva argues that the 936 Patent is a selection patent, but that the criteria for a valid selection patent are not satisfied.

[149] Claims 37 and 69 are reproduced here:

> 37. The compound of claim 26 selected from the group consisting of:
>
> N-(4-morpholine)carbonyl-(3-(1-naphthyl)-L-alanine-L-leucine boronic acid,

> N-(8-quinoline)sulfonyl-(3-(1-naphthyl)L-alanine-L-leucine boronic acid,
>
> N-(2-pyrazine)carbonyl-L-phenylalanine-L-leucine boronic acid,
>
> N-(2-quinoline)sulfonyl-L-homophenylalanine-L-leucine boronic acid,
>
> N-(3-Pyridine)carbonyl-L-phenylalanine-L-leucine boronic acid, and
>
> N-(4-Morpholine)carbonyl-L-phenylalanine-L-leucine boronic acid.
>
> 69. The compound N-(2-pyrazine)carbonyl-L-phenylalanine-L-leucine boronic acid, or a pharmaceutically acceptable salt or boronate ester thereof.

[150] As already indicated, claim 69 defines bortezomib while claim 37 defines bortezomib and five other compounds.

[151] It should be noted that the validity of the 936 Patent, as well as corresponding foreign patents, has been considered previously in a number of court decisions. As stated in paragraph [3] above, Justice Barnes concluded in an application under the *Regulations* that the claims of the 936 Patent that were in issue before him (including claim 69) were obvious. Teva urges me to follow Justice Barnes' conclusion.

[152] Outside Canada, Millennium draws my attention to three European decisions which concluded provisionally that the European patent that corresponds to the 936 Patent is not obvious. These decisions are (i) a judgment of the District Court of The Hague dated July 25, 2017 (*Millennium Pharmaceuticals Inc v Teva Nederland BV et al*), (ii) an order of the District Court Dusseldorf dated July 28, 2017 (*Millenium* [*sic*] *Pharmaceuticals Inc v*

Ratiopharm GmbH), and (iii) a decision of the Maritime and Commercial High Court of Denmark dated November 3, 2017 (*Millennium Pharmaceuticals Inc v Teva Denmark A/S et al*).

[153] The parties are agreed that I may consider all of these prior Canadian and European decisions for their persuasive qualities, but I am not bound by any of them.

[154] I turn now to an analysis of the steps to be taken in assessing obviousness as set out in paragraph [82] above.

(1) Person Skilled in the Art

[155] The parties appear to be agreed that the skilled person to whom the 936 Patent is addressed is a team comprising a medicinal chemist with experience in boronic acid chemistry and a biochemist having experience with the proteasome and peptide chemistry.

(2) Common General Knowledge

[156] Much of the common general knowledge applicable to the 936 Patent is identified on the first page thereof, some of which is listed in paragraph [40] above. This common general knowledge includes synthesis of N-terminal protected peptidyl boronic ester and acid compounds, and their effectiveness at inhibiting proteolytic enzymes (proteases) and growth of cancer cells.

[157] The 904 Application referenced on the first page of the 936 Patent addresses inhibition of the proteasome and is therefore the most relevant prior art reference. It is discussed in greater detail below.

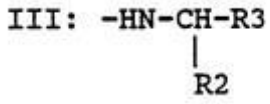
[158] Other common general knowledge is discussed in paragraphs [7] to [17] above in the Background to the Patented Technologies section.

(a) *The 904 Application*

[159] The 904 Application is entitled "Chymotrypsin-Like Proteases and their Inhibitors" and was published in 1991. The 904 Application concerns the identification, characterization and purification of two proteases, chymase and the proteasome (there called the multicatalytic protease).

[160] The 904 Application describes a broad genus of protease inhibiting peptidyl compounds. Page 4 describes a Formula II: R-A4-A3-A2-Y, where:

1. Y may be:



   in which R2 may be isobutyl and R3 may be a boronic acid residue. In that event, Y is boroleucine (boronic acid with a Leu side chain), just as in bortezomib.
2. A2 may be an amino acid selected from the group which contains phenylalanine, just as in bortezomib.

3. A3 and A4 may be amino acids or they may be simple covalent bonds, in which case A2 is bonded directly to R. In the latter event, the formula defines a dipeptide analog, like bortezomib. Otherwise, the formula could define a tripeptide or a tetrapeptide.
4. R may be an N-terminal blocking group. The definition of "N-terminal blocking group" in the 904 Application includes:

> an arylcarbonyl, alkylcarbonyl, alkoxycarbonyl, aryloxycarbonyl, aralkyloxycarbonyl, aralkylsulfonyl, alkylsulfonyl, or arylsulfonyl peptide protecting group, or other equivalents known to those skilled in the art of peptide synthesis and which are known to protect molecules from degradation by aminopeptidases (Gross and Meienhofer, eds., The Peptides, vol. 3, Academic Press, New York, 1981 pp. 3-81, describes numerous suitable amine protecting groups).

[161] Millennium does not dispute the information in the previous paragraph. But it does argue the following:

1. The number of compounds contemplated in the 904 Application is so great (Dr. Snow says trillions), and only one test result concerning inhibition of the proteasome by a boronic acid analog is provided, that a skilled person could not predict that the boronic acid compounds defined in claims 37 and 69 of the 936 Patent would be effective inhibitors of the proteasome; and
2. The definition of "N-terminal blocking group" in the 904 Application does not encompass pyrazine carbonyl as is present in bortezomib.

[162] The first point is addressed in the "Obviousness" section below. I will deal with the second point here.

[163] Teva argues that pyrazine carbonyl falls within the definition of "N-terminal blocking group". It supports this argument in two ways:

1. Teva argues that pyrazine carbonyl is an arylcarbonyl which is explicitly included within the definition. An arylcarbonyl involves a ring that is similar to pyrazine carbonyl. However, pyrazine carbonyl is actually a heteroaryl in that its ring contains two nitrogen atoms.
2. Teva also argues that, even if pyrazine carbonyl were not considered to be an arylcarbonyl, it would be considered among the "other equivalents known to those skilled in the art of peptide synthesis and which are known to protect molecules from degradation by aminopeptidases", as contemplated in the definition of "N-terminal blocking group".

[164] With regard to the first of these arguments, Teva's expert Dr. Bachovchin cited a definition of "aryl" in a well-accepted source, the IUPAC (International Union of Pure and Applied Chemistry) Gold Book, which indicates that heteroaryl groups are sometimes subsumed within the term "aryl".

[165] Millennium responds by noting that the 904 Application itself explicitly defines the term "aryl", and it is therefore unnecessary and inappropriate to look to a general definition of this term. The 904 Application states that:

> "aryl" means an aromatic moiety, e.g., phenyl, of 6 to 18 carbon atoms, unsubstituted or substituted with one or more alkyl, substituted alkyl, nitro, alkoxy or halo groups;"

[166] The parties appear to be agreed that this definition excludes pyrazine carbonyl.

[167] In view of the definition provided in the 904 Application itself, I agree with Millennium that pyrazine carbonyl does not fall within the definition of arylcarbonyl as used therein.

[168] I turn now to Teva's argument that pyrazine carbonyl is among the equivalents contemplated in the definition of "N-terminal blocking group". Millennium notes that such equivalents must be "known to protect molecules from degradation by aminopeptidases". Millennium also notes that the Gross and Meienhofer reference to which the definition refers does not include pyrazine carbonyl among known blocking groups, although it does list other heteroaryl blocking groups. It argues that listing some heteroaryls but not pyrazine carbonyl makes it clear that pyrazine carbonyl is not included.

[169] I disagree with this argument. In my view, the definition of "N-terminal blocking group" is clearly intended to be broad. Though it does not include heteroaryls within the scope of aryls that are expressly contemplated as part of the definition, the broad range of possible N-terminal blocking groups that are expressly contemplated, together with the reference to known equivalents, leaves room for pyrazine carbonyl, provided it can be shown to be "known to protect molecules from degradation by aminopeptidases". I have been given no adequate reason to find that the authors of the 904 Application would have chosen to define "N-terminal blocking group" in such broad terms, but to exclude pyrazine carbonyl.

[170] Dr. Bachovchin identified five prior art references in which pyrazine carbonyl was described for use in protecting peptides from degradation:

1. Kocevar et al, “Syntheses of some N-(pyrazinecarbonyl) amino acids and peptides” (1988) 107:5 Recl Trav Chim Pays-Bas 366-369;
2. Kayahara et al, “N-Protected Tripeptide Inhibitors of Angiotensin Converting Enzyme” (1990) 54:5 Agric Biol Chem 1325-1326;
3. “Method of making peptides”, US Patent No 5169935 8 December 1992;
4. Ghosh et al, “Potent HIV Protease Inhibitors: The Development of Tetrahydrofuranylglycines as Novel P2-Ligands and Pyrazine Amides as P3-Ligands” (1993) 36:16 J Med Chem 2300-2310; and
5. “HIV protease inhibitors”, European Patent Application No 0 490 667 17 June 1992.

[171] Millennium argues that pyrazine carbonyl is not a usual choice for an N-terminal blocking group. However, this is relevant to consideration of whether its use in bortezomib was obvious, not to the question of whether pyrazine carbonyl is among the N-terminal blocking groups that were “known to protect molecules from degradation by aminopeptidases” as defined in the 904 Application. The prior art cited by Dr. Bachovchin indicates that pyrazine carbonyl was indeed a known N-terminal blocking group for use in protecting peptides. I note also that Dr. Adams acknowledged in cross-examination that pyrazine carbonyl was known and commercially available at the time of his research.

[172] Accordingly, I conclude that pyrazine carbonyl falls within the scope of N-terminal blocking groups contemplated in the 904 Application.

[173] Based on my earlier conclusions that the 904 Application also contemplates a dipeptide analog having boroleucine at P1 and Phe at P2, it follows that bortezomib falls within the broad genus of compounds contemplated in the 904 Application.

[174] This, by itself, is not sufficient to conclude that the claims in issue of the 936 Patent are invalid for obviousness. However, it does mean that the 936 Patent is effectively a selection patent and must meet the requirements for validity thereof. This issue is addressed in the "Obviousness" section below.

[175] Other prior art references cited in the 936 Patent and mentioned in paragraph [40] above also describe a broad range of protease inhibitors that, in Teva's submission, encompass bortezomib. These include the 082 Patent and the 948 Patent. However, these patents do not address the proteasome specifically as does the 904 Application. Therefore, the 904 Application is the most important prior art reference in the context of Teva's allegation of obviousness of the 936 Patent, and it is unnecessary to discuss the 082 and 948 Patents further.

(3) Inventive Concept

[176] There is no dispute that the inventive concept is determined by reference to the claims. Different claims may have different inventive concepts.

[177] The parties are also agreed that the inventive concept of claims 37 and 69 is simply the compounds defined thereby. Accordingly, the inventive concept of claim 69 is bortezomib. Bortezomib is also part of the inventive concept of claim 37.

(4) Differences between the State of the Art and the Inventive Concept

[178] Based on the foregoing analysis, I conclude that the difference between the state of the art and the compounds of the inventive concepts of claims 37 and 69 is found in the fact that bortezomib, despite falling within the scope of compounds contemplated in the prior art, was not identified prior to the 936 Patent. No one had made the selection of components that are characteristic of bortezomib: (i) boronic acid warhead, (ii) dipeptide, (iii) Leu side chain at P1, (iv) Phe at P2, and (v) pyrazine carbonyl as the N-terminal blocking group.

(5) Obviousness

[179] As indicated above, an invalid selection is not an independent ground of invalidity, but the conditions for a valid selection patent serve to characterize the patent and accordingly inform the obviousness analysis.

[180] Though the obviousness of bortezomib, and hence of claims 37 and 69, is properly considered with a view to the combination of all of the characteristic components thereof listed in paragraphs [27] and [178] above, it is convenient to address each individually first.

(a) *Boronic Acid Warhead*

[181] Millennium acknowledges that boronic acid was among the known options for a warhead. However, Millennium argues that a skilled person would not have been inclined to try a boronic acid warhead because of its known toxicity. Dr. Adams stated that the conventional wisdom in the scientific community was that boron-containing inhibitors were not developable. At the time, there were no boron-containing compounds approved as drugs.

[182] Millennium also notes that, to the extent that the skilled person would have considered the 904 Application, s/he would have noted that the aldehyde that was tested against the proteasome showed greater potency than the boronic acid.

[183] The evidence indicates that, at the claim date of the 936 Patent, only two types of warheads were known to inhibit the proteasome: aldehydes and boronic acids. It was also known that aldehydes had shown poor selectivity. Moreover, some prior art showed boronic acids to be much more potent inhibitors of certain types of proteases. The inventors also tested trifluoromethyl ketones and chloromethyl ketones, but these were not useful as proteasome inhibitors.

[184] I do not accept Dr. Adams' statement that boron-containing compounds were considered not developable as proteasome inhibitors. Firstly, he offered no documentary support to corroborate this statement. More importantly, neither of the other inventors of the 936 Patent who testified, nor any of the expert witnesses, shared this view. Moreover, Dr. Snow acknowledged that BI put considerable resources into pursuing boron-containing compounds in the early 1990s. In my view, any concerns about the toxicity of boron that may have existed at the time were not sufficient to dissuade the skilled person from trying boronic acid as a warhead.

[185] In my view, it was obvious to the skilled person to try boronic acids as proteasome inhibitors. I reach this conclusion based on (i) the 904 Application, which describes a boronic acid proteasome inhibitor, and (ii) Dr. Stein's evidence that he conceived the idea of trying boronic acid proteasome inhibitors shortly after joining MyoGenics based on the available literature. I consider also the limited number of types of promising warheads, and the limited

amount of work required to test their potency. The skilled person could not know for certain that boronic acids would be potent as proteasome inhibitors until they were tested, but such testing would be straightforward and routine.

(b) *Dipeptide*

[186] Relying on Dr. Snow's testimony, Millennium argues that there is nothing in the prior art showing dipeptide inhibitors of the proteasome having been tested. The sole boronic acid that was tested against the proteasome in the 904 Application was a tetrapeptide.

[187] As noted in paragraph [28] above, though tripeptides and tetrapeptides are generally more potent than dipeptides, they are generally more difficult to synthesize, less soluble, less metabolically stable and less able to penetrate cells. Moreover, the process of synthesizing a tripeptide or a tetrapeptide involves first synthesizing a dipeptide. Dr. Snow acknowledged that such a dipeptide would normally be tested as part of the testing of a related tripeptide of tetrapeptide. He also acknowledged that the 904 Application states that dipeptides would work to inhibit the proteasome. Finally, he acknowledged that a dipeptide would have been obvious to try.

[188] There is no indication in the 936 Patent that the inventors made any surprising discovery of a dipeptide that was more potent than the tripeptide. Rather, the inventors' first test with a tripeptide revealed such high potency that they decided that there was potency to spare. Accordingly, the inventors chose to accept the disadvantage of the reduced potency of the dipeptide in exchange for expected advantages such as ease of manufacture, solubility, stability and cell penetration.

[189] In my view, there was nothing inventive in the selection of a dipeptide. Once it had been decided to test boronic acids, the skilled person would likely have started with tripeptides, but would have synthesized and tested dipeptides as a matter of course. This testing would have revealed good potency for dipeptides, and prompted further testing of dipeptides.

(c) *Leu Side Chain at P1*

[190] As regards the selection of Leu at P1, Teva relies principally on a statement in the 904 Application at page 51 that the proteasome prefers Leu at P1.

[191] Millennium argues that the data in the 904 Application does not support this statement. I disagree. The statement appears to be a reference to the first five of the compounds whose test results are shown in Figure 14 of the 904 Application. These five compounds are all the same except for P1. Leu at P1 gave the best results.

[192] Dr. Adams also acknowledged that the prior art literature pointed to Leu at P1. Dr. Vinitsky agreed that Leu might have been among the first choices tested at P1. Dr. Snow was reluctant to accept that it was more or less self-evident to choose Leu at P1, but he acknowledged having said just that in his affidavit before this Court in the application under the *Regulations* in relation to the 936 Patent.

[193] In light of the literature, including the above-mentioned statement in the 904 Application, I conclude that there was no invention in selecting Leu at P1. The fact that there were other known options at P1 does not change this.

(d) *Phe at P2*

[194] Millennium notes that the only example of a boronic acid inhibitor of the proteasome tested in the 904 Application had Lysine at P2. Moreover, the same passage in the 904 Application that indicates a preference for Leu at P1 also indicates a preference for Arginine at P2. Referring to Dr. Snow's evidence, Millennium cites prior art indicating preferences for Leucine or Alanine at P2. Dr. Snow concluded that there was no clear consensus in the prior art for P2.

[195] The parties seem to be agreed that several amino acids would work at P2. The immediate question is whether it was inventive to select Phe from those options. To assess this, it is reasonable to consider that Dr. Snow accepted that the prior art at the time indicated a preference for a hydrophobic amino acid at P2 and that there were a limited number of options (less than ten). Dr. Bachovchin and Dr. Wilk had similar views. Phe is a hydrophobic amino acid.

[196] It is also relevant to consider whether the selection of Phe over those other known hydrophobic amino acids was inventive. One way to show this would be with better results for Phe than for the other known options. That argument has not been made to me. In fact, Dr. Adams acknowledged that Phe at P2 did not outperform any other amino acid at P2.

[197] Millennium argues that the validity of a selection patent should be assessed in relation to what was known from the prior art, and that it is inappropriate to make comparisons between compounds based on test results obtained by the inventors. While it is true that the applicable prior art is that which was known before the patent in suit, the issue here is not whether the compounds in question are encompassed within the prior art. I have already concluded that

bortezomib, and many other related peptidyl boronic acid compounds, are encompassed by the prior art. Rather, the issue here is whether there was something inventive in selecting the characteristic components of bortezomib from among the other options. In that context, I see no impropriety in comparing test results obtained by the inventors.

[198] Teva cites the analogy of the 5¼" plate that was discussed by Jacob L.J. in *Actavis UK Limited v Novartis AG*, [2010] EWCA Civ 82 (UK CA) at paras 36-38. Jacob L.J. referred to a plate of a size that is novel (in that no plate of that size has ever been made) and arguably non-obvious since nothing in the prior art suggests that size. Such a plate cannot be patentable because its size is arbitrary and non-technical. Similarly, the evidence in the present case indicates that the choice of Phe at P2 was similarly arbitrary and non-technical. There appears to be no advantage in selecting Phe over other known options.

[199] In the end, I have heard no adequate reason to conclude that the selection of Phe at P2 was inventive. Recognizing that Teva bears the burden of establishing obviousness, I am satisfied that it would have been obvious to try Phe at P2. Phe was among a limited number of hydrophobic amino acids that were preferred and that a skilled person would have tested and in respect of which good results would have been expected. Moreover, the testing would have been straightforward and routine.

(e) *Pyrazine Carbonyl as the N-Terminal Blocking Group*

[200] The analysis of the selection of pyrazine carbonyl as the N-terminal blocking group is similar to that for the selection of Phe at P2. Pyrazine carbonyl was known in the prior art as an N-terminal blocking group and, as discussed above, was encompassed within the many

N-terminal blocking groups contemplated in the 904 Application. The question is whether there was anything inventive in the selection of pyrazine carbonyl from among the available options.

[201] Contrary to the situation with the selection of Phe at P2, there were many more N-terminal blocking group options to choose from that would have been expected to yield good results. However, it appears that the work of the inventors did not reveal pyrazine carbonyl to offer better results than other N-terminal blocking groups. Table II in the 936 Patent shows a number of the compounds that were tested *in vitro* for proteasome inhibition. 11 of those had the same characteristic components as bortezomib except for the N-terminal blocking group. Of these 11 compounds, nine had greater potency than bortezomib. No tests for selectivity are reported in the 936 Patent for any of these nine more potent compounds. There also is no suggestion in the 936 Patent that the choice of pyrazine carbonyl was advantageous in any other way.

[202] As with the selection of Phe at P2, I have heard no adequate reason to conclude that the selection of pyrazine carbonyl as an N-terminal blocking group was inventive. Despite the greater number of options, it remains the case that there were a finite number of identified predictable solutions known to a skilled person. The 936 Patent does not provide any unexpected results.

(f) *Conclusion on Obviousness*

[203] Having now considered each of the characteristic components of bortezomib individually, I must now consider whether it was inventive to have selected all of them in combination. In my view, it was not. I have already concluded that the selection of each of the

components individually was not inventive, and there is nothing in the combination of these components that prompts me to conclude that the selection of all of them together was any less obvious. There are a finite number of possible practical combinations to try, and any of them would have been expected to offer some potency. The testing involved would have been routine and there was nothing inventive in the decision to conduct such testing.

[204] Turning now to the list of conditions for a valid selection patent (see paragraph [89] above), I am not convinced that they are met. Though bortezomib is unquestionably a potent inhibitor of the proteasome which is effective in the treatment of certain types of cancer, it is not clear that this advantage is peculiar to bortezomib or to the other compounds defined in claim 37. Neither the 936 Patent nor the evidence adduced at trial supports a conclusion that bortezomib (or the other compounds defined in claim 37) performs better than the many similar compounds that were considered by the inventors and which offered excellent potency in *in vitro* tests. Though the evidence indicates that the inventors tested 150-200 compounds, it does not appear that the results of these tests led to the selection of bortezomib. For example, Tables IV and V report results of selectivity testing. Of the 93 compounds whose potency is reported in Table II, six are tested for selectivity and reported in Tables IV and V. The potency of these six compounds ranges from 0.035 nM to 1.7 nM. However, Table II lists, by my count, 36 other compounds whose potency is better than 1.7 nM. It is not clear how the inventors of the 936 Patent made their selection of candidates for further testing, but it does not appear to have been based on good potency results.

[205] Similarly, it does not appear that potency within cells, as reported in Table VI, was the driver in the selection of the three compounds tested in mice, whose results are reported in Table

VII. The potency results as reported in Table VI for the three compounds that were tested in mice were 738 nM, 210 nM and 69 nM. However, 25 other compounds of the 47 tested in Table VI report potency better than 738 nM.

[206] In my view, the third condition for a valid selection patent is not met. The selection is not "in respect of a quality of a special character peculiar to the selected group."

[207] To sum up, a valid patent must describe and claim something that a skilled but unimaginative technician would not have come to directly and without difficulty, something that requires inventive ingenuity. Certainly, many tests had to be conducted before deciding on bortezomib for Millennium's commercial product, but I am unable to find anything in the 936 Patent that falls outside what the unimaginative skilled technician would have found without the exercise of inventive ingenuity.

[208] I conclude that claims 37 and 69 of the 936 Patent are invalid for obviousness.

[209] In my view, the issue of commercial success cannot save these claims from obviousness. There is little doubt that the 936 Patent was not sufficient to create a commercially successful product. Bortezomib alone is too unstable to be commercially practical. This is evidenced by the long time period between the filing of the application for the 936 Patent in 1995, and the introduction of Velcade to the market in 2005. It is notable that in 1999, when Millennium acquired Leukocyte, no value was placed on bortezomib.

[210] In my analysis of Teva's allegations of obviousness of claims 37 and 69 of the 936 Patent, I have not found it necessary to make reference to the portion of Dr. Bachovchin's testimony in which he recounted a conversation with Dr. Adams before the claim date. I will describe this alleged conversation and make a comment thereon even though it is not necessary to my decision.

[211] Dr. Bachovchin related that Dr. Adams approached him (possibly in 1994) for his thoughts on the idea of using boronic acids as proteasome inhibitors. Dr. Bachovchin testified that he told Dr. Adams that he expected that boronic acids would be potent inhibitors, but that it would be necessary to use a dipeptide in order to avoid a prior patent owned by DuPont. He continued that he also made suggestions for other characteristic components of a proteasome inhibitor that pointed directly to bortezomib. Dr. Bachovchin also testified that he even drew his suggested molecule on a chalkboard.

[212] Dr. Adams denied that the conversation in question ever took place.

[213] The parties made submissions as to why I should believe Dr. Bachovchin's version of events or Dr. Adams' version. I need not, and will not, state a conclusion in this regard. However, I do wish to note that Dr. Bachovchin's version of events is undocumented and uncorroborated. It relies solely on Dr. Bachovchin's recollection of a discussion some 24 years ago. I share the concern that Justice Barnes expressed in *Novopharm Limited v Eli Lilly and Company*, 2010 FC 915 at para 84, that there is a real danger in accepting such evidence. I am not concluding that the conversation in question did not take place, but I would be reluctant to accept the details related by Dr. Bachovchin (without more) to find a patented invention obvious.

B. *146 Patent: Obviousness*

[214] As with the 936 Patent, Teva alleges that certain claims of the 146 Patent (claims 30, 45, 46 and 81-84) are invalid for obviousness. Claim 30 is an independent claim and is reproduced here:

> 30. The lyophilized compound D-mannitol N-(2-pyrazine)carbonyl-L-phenylalanine-L-leucine boronate.

[215] The compound defined therein is bortezomib mannitol ester.

[216] Claim 45 is a dependent claim that reads as follows:

> 45. The method of claim 33, wherein the compound of formula (1) is D-mannitol N-(2-pyrazine)carbonyl-L-phenylalanine-L-leucine boronate.

[217] The compound defined in claim 45 is bortezomib mannitol ester, just as in claim 30. Claim 33, from which claim 45 depends, defines a method of preparing a lyophilized compound of formula (1). For the purposes of this decision, it is not necessary to discuss claim 33 in detail.

[218] Claim 46, another dependent claim, is reproduced here:

> 46. The method of claim 44, wherein the compound of formula (3) is N-(2-pyrazine)carbonyl-L-phenylalanine-L-leucine boronic acid.

[219] The compound identified in claim 46 is bortezomib. Claim 44, from which claim 46 depends, defines a number of compounds, including bortezomib, and is itself dependent on the method of claim 33. Formula (3) is one of the starting compounds of the method of claim 33.

Since the starting compound of the method is bortezomib, it follows that the resulting compound will be bortezomib mannitol ester.

[220] Claim 81 is a composition claim which is reproduced here:

> 81. A composition comprising (i) the compound of any one of claims 1-32 and 54-57 and (ii) a pharmaceutically-acceptable carrier.

[221] Among the claims from which claim 81 depends is claim 30, which has been discussed above.

[222] Claim 82 is another composition claim. It reads as follows:

> 82. A composition comprising (i) the compound of formula (1) prepared in accordance with the method of any one of claims 33-53 and (ii) a pharmaceutically-acceptable carrier.

[223] Among the claims from which claim 82 depends are claims 45 and 46, which have been discussed above.

[224] Claim 83, reproduced here, depends from claim 30, among others:

> 83. A lyophilized cake comprising the compound of any one of claims 1-32 and 54-57.

[225] Claim 84, reproduced here, depends from claims 45 and 46, among others:

> 84. A lyophilized cake comprising the compound of formula (1) prepared in accordance with the method of any one of claims 33-53.

[226] Before entering into the analysis of the issue of obviousness, it is useful to note that the 146 Patent and its corresponding US patent have been considered by the courts previously. As mentioned at the beginning of these reasons, Justice Barnes, in the context of an application under the *Regulations*, concluded that claim 30 of the 146 Patent was invalid for obviousness. As with the 936 Patent, Teva urges me to follow Justice Barnes' conclusion.

[227] In the US, a District Court ruled that the claims in issue of the corresponding US patent were invalid for obviousness. However, on appeal, the US Court of Appeals for the Federal Circuit (CAFC) reversed the District Court decision. Millennium urges me to follow the reasoning of the CAFC.

[228] Just as with the 936 Patent, the parties are agreed that these decisions may be persuasive but are not binding on me.

[229] I turn now to the analysis of the issues relevant to assessing obviousness.

(1) Person Skilled in the Art

[230] The parties have an important disagreement on the characteristics of the skilled person. They agree that the 146 Patent is addressed to a pharmaceutical formulator with a degree in pharmaceutical sciences and experience in the field. But Teva argues that the skilled person is in fact a team which also comprises a medicinal chemist whom its expert Dr. Bachovchin described as having "a graduate degree in chemistry, biochemistry, or a related discipline, and at least a few years['] experience working in a laboratory engaged in the study of proteolytic enzymes and their inhibitors."

[231] Millennium counters that the 146 Patent is addressed to the formulator alone. It refers to the title of the 146 Patent ("Formulation of Boronic Acid Compounds") and argues that the bulk of the patent, including the Field of the Invention section and the Summary of the Invention section, relates to the formulation of stable pharmaceutical compositions. It also argues that the formulator would have an adequate understanding of chemistry to assess the prior art, and could consult a medicinal chemist if it became necessary.

[232] For its part, Teva notes that the first aspect of the invention described in the 146 Patent (at paragraph 7 thereof) is a genus of compounds having formula (1), which includes bortezomib mannitol ester. This aspect of the invention does not refer to formulation or lyophilisation.

[233] Teva also points to paragraph 101 of the 146 Patent which indicates that the compounds and compositions according to aspects of the invention may be prepared by transesterification or by incorporation of the sugar moiety at an earlier stage of the synthesis. These methods of preparing compounds and compositions are directed to a medicinal chemist.

[234] Teva also notes that Millennium's own expert Dr. Snow acknowledged, albeit reluctantly, that the skilled person of the 146 Patent includes a medicinal chemist.

[235] The parties' dispute concerning the skilled person does not substantially affect the prior art of which that person would have been aware. As discussed in greater detail below, the parties are agreed on a key point – that the skilled person would have been aware that lyophilizing a solution of bortezomib and mannitol could result in a reaction forming a mannitol ester. Instead, the practical effect of the parties' dispute as to whether the skilled person of the 146 Patent

includes a medicinal chemist seems to be in relation to whether the skilled person, being aware that an ester might form, would avoid trying lyophilisation with mannitol. Millennium's argument is that a formulator's task is to create a practical formulation of the compound that s/he has been given, and the formulator will therefore avoid taking steps that may change the compound, such as by formation of an ester. The medicinal chemist, on the other hand, routinely creates new compounds and is less reticent to change the compound.

[236] One point to bear in mind here is that the skilled person is not defined claim-by-claim as is the inventive concept. A patent is read, and its claims are construed, from the point of view of the skilled person in the context of the patent as a whole. There cannot be different skilled persons for different claims. The fact that some claims of a patent are not asserted cannot affect the characteristics of the skilled reader of the patent. (See Justice Barnes' comments on this issue in his NOC decision on the 146 Patent, *Janssen Inc v Teva Canada Limited*, 2015 FC 184 at para 92.)

[237] Even though the 146 Patent is largely about preparing pharmaceutical formulations, it is not exclusively so. At least paragraph 101 and claims 1-15 of the 146 Patent contemplate a skilled person with a perspective broader than a formulator. Some of what is described and claimed in the 146 Patent encompasses subject matter that is beyond the knowledge of a formulator. In my view, the skilled person of the 146 Patent is a team comprising both a pharmaceutical formulator and a medicinal chemist.

(2) Common General Knowledge

[238] As indicated in paragraph [45] above, the information contained in the 936 Patent was known at the claim date of the 146 Patent. Accordingly, boronic acid and ester compounds, including bortezomib, were known.

[239] Paragraph 4 of the 146 Patent cites prior art indicating that alkylboronic acids, like bortezomib, are difficult to obtain in analytically pure form. They readily form boroxines under dehydrating conditions. Also, alkylboronic acids and their boroxines are also often air-sensitive. These difficulties limit the pharmaceutical utility of such compounds.

[240] Paragraph 5 states that there is a need for improved formulations of boronic acid compounds as regards convenience of preparation, stability, shelf life and bioactivity when administered.

[241] Based on Wu 2000, degradation pathways for bortezomib, including oxidation, had been described in the prior art (see paragraph [49] above). Wu 2000 revealed that bortezomib was unstable in various aqueous solutions.

[242] It was well-known to use lyophilisation to address aqueous instability. It was also well-known to use this technique for injectable medications in order to extend shelf-life, and then reconstitute the lyophilized compound shortly before injection. According to Dr. Suryanarayanan, this approach was common for peptide drugs.

[243] Because bortezomib was so potent, and hence only a small amount would be used in a dose, the skilled person would have known that a bulking agent would be required. Though there were several to choose from, one of the most common bulking agents, then and now, was mannitol.

[244] As mentioned in the previous section, the parties agree that the skilled person would be aware that lyophilizing a solution of bortezomib and mannitol could result in the formation of an ester. Dr. Anderson opined that this potential for ester formation would eliminate one of the desired characteristics of a bulking agent, inertness, and make mannitol a non-starter as a bulking agent for bortezomib.

[245] Teva responds by relying on the evidence of Dr. Bachovchin to the effect that the skilled person knew that, generally speaking, the formation of esters with boronic acids and mannitol was readily reversible. The process of reversing esters to boronic acids is called hydrolysis. Some of the data in the 936 Patent supports Dr. Bachovchin's assertion of ready reversibility. He compared potency results in Table II thereof for boronic acid peptides to their corresponding esters. Similar potency results indicate ready reversibility of the ester formation. In one case, the potency of the boronic acid and the ester were quite different, but Dr. Bachovchin explained that this result was an artifact of the dilution and not indicative of difficulty hydrolyzing. Dr. Snow acknowledged that a skilled person would expect that an ester of boronic acid would likely hydrolyze to some extent under mild conditions.

[246] Teva argues that, because it would be expected that any ester formation would be readily reversible, the skilled person would not be deterred from trying mannitol as a bulking agent.

Teva also argues that the skilled person would even see an advantage to ester formation as a means of preventing boroxine formation. The formation of the ester changes the C-terminus of the bortezomib molecule, which is the location at which bortezomib molecules bond to form a boroxine. I accept that ester formation impedes boroxine formation.

[247] I also accept Teva's position that any concern that a skilled person might have that mannitol as a bulking agent with boronic acid might not be inert would be balanced by the expectation that any ester formation would be readily reversible.

[248] Millennium also argues that mannitol was known to crystallize out of solution during lyophilisation which could cause problems. Teva responds that this tendency was more of a concern for proteins than for shorter peptides like bortezomib. Moreover, there were known lyoprotectants that could be used to prevent such crystallization.

[249] Finally, it should be noted that the skilled person would not have expected that only one type of ester would form. The parties seem to be in agreement that there are several different esters that can form with bortezomib and mannitol (several different locations on the mannitol molecule that can bond with the C-terminus of bortezomib), and the skilled person would have expected a mix of these to form. Unexpectedly, only a single ester was formed. I accept Millennium's submission that a multiplicity of different esters would compound challenges of characterization of the formulation.

(3) Inventive Concept

[250] Unlike the case of the 936 Patent, the parties are not in complete agreement on the inventive concept of the claims in issue of the 146 Patent. That said, the difference is not huge. They disagree on the extent to which the properties of the compounds in the claims form part of the inventive concept.

[251] Teva's experts Drs. Bachovchin and Suryanarayanan and Millennium's experts Drs. Anderson and Snow substantially agreed that the inventive concept of claim 30 of the 146 Patent is the lyophilized compound bortezomib mannitol ester. Drs. Anderson and Snow added that the inventive concept also includes the properties associated with the compound. Drs. Bachovchin and Suryanarayanan acknowledged that the compound has stability acceptable for use in pharmaceutical preparations, but they made no such acknowledgement as regards the properties of solubility and dissolution rate. Teva argues that these properties are realized in Millennium's commercial Velcade formulation by virtue of a large excess of mannitol which is not referred to or inherent in the compound defined in claim 30.

[252] I agree with Teva. The inventive concept of claim 30 is lyophilized bortezomib mannitol ester with its improved stability. This much is inherent in the compound. However, the properties of improved solubility and dissolution rate depend on a particular formulation to which claim 30 is not limited.

[253] The lyophilized compound bortezomib mannitol ester is also defined in, and therefore part of the inventive concept of, each of claims 45, 46 and 81-84. None of these claims defines

an excess of mannitol. Hence, the inventive concept of these claims also does not include properties of solubility or dissolution rate.

(4) Differences between the State of the Art and the Inventive Concept

[254] The state of the art at the claim date included the 936 Patent which describes bortezomib as well as esters of several boronic acid compounds, though no ester of bortezomib is explicitly discussed. Mannitol was well known as a bulking agent, but it had not been used as such with bortezomib.

[255] Though mannitol had also not been used in the formation of an ester of bortezomib, it was used in the formation of an ester of another boronic acid as described in PCT Application Publication No. WO 00/57887 (the 887 Application). Example 7 thereof describes the formation of a complex (an ester) of mannitol and L-p-boronophenylalanine. It also describes the lyophilisation of that complex. Millennium distinguishes the 887 Application by noting that the ester is formed before lyophilisation. Millennium argues that ester formation in the 146 Patent takes place during lyophilisation. However, this seems to be a meaningless distinction in view of the position of Teva and of Millennium's expert Dr. Anderson, with which I agree, that claim 30 encompasses lyophilized bortezomib mannitol ester regardless of whether the ester is formed during the lyophilisation or before.

[256] Millennium also distinguishes the 887 Application because it concerns arylboronic acids, which are structurally different, and have different properties, from bortezomib, which is an alkylboronic acid. Millennium also notes that the 887 Application addresses solubility issues rather than oxidative instability, and that it involves changes in pH. I am not convinced that these

differences are such that a skilled person would have ignored or been unaware of the 887 Application and its disclosure of lyophilisation and the formation of an ester of a boronic acid.

[257] The difference between the state of the art and the inventive concept of the lyophilized bortezomib mannitol ester compound is the use of mannitol and lyophilisation to form an ester of bortezomib.

(5) Obviousness/Obviousness to Try

[258] The last step in the analysis of obviousness asks whether, viewed without any knowledge of the alleged invention as claimed, the difference between the state of the art and the inventive concept constitutes a step which would have been obvious to the skilled person or would have required any degree of invention.

[259] Because the 146 Patent concerns an area of endeavour "where advances are often won by experimentation, where there may be numerous interrelated variables with which to experiment", it is appropriate to apply the "obvious to try" test. As indicated in paragraph [83] above, a finding that an invention was "obvious to try" requires evidence to convince a judge on a balance of probabilities that it was more or less self-evident to try to obtain the invention.

[260] In this case, the question is whether it was more or less self-evident to try to form lyophilized bortezomib mannitol ester.

[261] Some factors to be considered are considered below.

(a) *Is it more or less self-evident that what is being tried ought to work? Are there a finite number of identified predictable solutions known to persons skilled in the art?*

[262] In this case, one question is whether it was more or less self-evident that lyophilized bortezomib mannitol ester ought to work to address the issue of instability of bortezomib.

[263] As indicated in paragraph [242] above, it was well-known to use lyophilisation to address aqueous instability. Of course, this is a general statement that does not take into account the other known possibility that lyophilizing a solution of bortezomib and mannitol could result in the formation of an ester (or several different esters). This possibility would introduce an additional uncertainty, but as indicated above, the skilled person would expect such ester formation to be readily reversible. The skilled person would also still expect improved stability as a result of lyophilisation.

[264] In my view, it was indeed more or less self-evident that what was being tried ought to work. It was not certain to succeed, but skilled person would have considered the probability good.

[265] I would have this view even if the inventive concept included properties such as improved solubility and dissolution rate. Dr. Suryanarayanan indicated that the introduction of mannitol to bortezomib would have been expected to improve dissolution rate regardless of whether an ester was formed. In addition, Dr. Bachovchin cited the Gross and Meienhofer reference mentioned in the 904 Application (Erhard Gross & Johannes Meienhofer, eds, *The Peptides: Analysis, Synthesis, Biology, Volume 3: Protection of Functional Groups in Peptide*

Synthesis (New York: Academic Press, 1981) at 19) for the expectation that esters of boronic acids would have improved solubility.

[266] The other question to ask as part of this factor is whether there are a finite number of identified predictable solutions known to skilled persons.

[267] The challenge addressed by the 146 Patent, as defined in paragraph 5 thereof, was to find formulations of boronic acid compounds that are conveniently prepared, bioactive when administered, and more stable than free boronic acid.

[268] There are indeed a finite number of ways to address this challenge. It is not necessary to identify them all. It is sufficient to note that lyophilisation was one way that would occur to the skilled person early in the process. Naturally, the formulator would prefer to make a ready-to-use formulation. Various techniques are available to attempt to improve stability of such a formulation such as refrigeration and the addition of excipients. However, failing an adequate ready-to-use formulation, it is my view that the skilled person would readily consider lyophilisation, as did the inventor Dr. Stella.

(b) *What is the extent, nature and amount of effort required to achieve the invention? Are routine trials carried out or is the experimentation prolonged and arduous, such that the trials would not be considered routine?*

[269] As indicated in paragraph [85] above, the issue of the actual course of conduct of the inventor may also be considered in this section.

[270] Millennium argues that a lot of work was done by the inventors over a two-year period from early 1997 to early 1999. This includes all the preliminary work that was done to develop a method of analysis, all of the liquid formulations that were attempted, and then the lyophilisation work.

[271] Teva argues that some of the work done by the inventors should not be considered because it was subsequently described in an article, Wu 2000, which is part of the prior art that is relevant to the 146 Patent. Teva argues that the skilled person would have the information in Wu 2000 and would therefore not have to repeat this work to arrive at the same invention. For its part, Millennium takes the position that consideration of the actual course of conduct is independent of the prior art that was available to the skilled person, and so the publication of Wu 2000 should not be considered for this purpose.

[272] No jurisprudence has been cited to me on this contentious point of whether publication of some of the inventors' work in the prior art renders it irrelevant to consideration of the inventors' actual course of conduct. However, in my view, I need not decide the issue. It is sufficient to note that, to the extent that the inventors' actual course of conduct has become part of the relevant prior art, it is less helpful in determining whether the solution provided by the inventors was obvious to try at the claim date. A skilled person at the claim date would have had more information and would not have had to go through the same steps, and make the same mistakes and chase the same wild geese, as the inventors did. What was not obvious to the inventors to try may well have been obvious to a skilled person at the claim date. The inventors' actual course of conduct may not indicate the challenges faced by the skilled person.

[273] Accordingly, no weight should be given in the present case to that part of the inventors' work that was published in Wu 2000.

[274] The work described in Wu 2000 is not the only work that was actually done by the inventors that is different from what a skilled person would have been expected to do. Contrary to his ordinary practice and the instructions he received, Dr. Stella did not arrange a literature search when he began his work in early 1997. He testified that a search was done only in August 1997. Even then, the search seems to have been lacking since it did not reveal the 936 Patent, which is clearly relevant and which had been published on May 9, 1996. It appears that corresponding PCT Application Publication No. WO 96/13266 was also published on the same date.

[275] As a result of the foregoing, the inventors of the 146 Patent were lacking information that the skilled person would have. Importantly, this includes information concerning the possible formation of an ester when bortezomib and mannitol are lyophilized. The parties agree that a skilled person would know about this, whereas Dr. Stella testified that he did not.

[276] It follows from this that the inventors' actual course of conduct is of limited assistance on the central issue of whether it would have been obvious to a skilled person to try lyophilisation of bortezomib with mannitol. Millennium seems to acknowledge this at paragraph 520 of its Trial Memorandum.

[277] Another important fact that limits the relevance of the amount of time and effort taken by the inventors is the fact that Dr. Stella first thought about trying lyophilisation relatively early in

his work (in July 1997). He took no steps in that direction until November, but that was only because Dr. Gupta, on whom Dr. Stella relied both for funding and for the supply of bortezomib for testing, was opposed to this approach. Once Dr. Stella began working on lyophilisation, he had the solution described in the patent within a month or two. An initial attempt using a substance known as PVP as a bulking agent was followed by a second, successful, attempt using mannitol. In my view, but for Dr. Gupta's opposition, the solution described in the 146 Patent would have been found months earlier.

[278] The inventors' time and effort after December 1997 is also of limited relevance because it consisted simply of verifying the stability of the new compound over time. This testing was routine.

[279] Finally, Teva makes a compelling argument that the amount of work actually done by the inventors may be higher than it would otherwise have been because the inventors' solubility target was repeatedly changed. Early in his work, Dr. Stella determined that bortezomib had a solubility of 0.5-0.6 mg/ml. His initial target for solubility of the formulation was 5 mg/ml. That target was subsequently reduced to 2.5 mg/ml, then to 2 mg/ml, and finally to 1 mg/ml. Accordingly, the mandate to improve solubility went from being a factor of 10 to a factor of 5 to a factor of 4 and finally to a factor of 2. I infer that the inventors' work would have progressed more efficiently if the target solubility had been 1 mg/ml from the beginning.

[280] Based on the foregoing, I conclude that the work to achieve the invention of the 146 Patent was mainly in the period from March to July 1997 (studying dissolution characteristics and possible ways of improving them), and in November and December 1997

(working on lyophilisation). It is true that the inventors did not know that they had obtained the desired stability until several months later, but the work involved in confirming this was simple and routine. In addition, the work that was published in Wu 2000 should be removed from the calculation, as should lost time due to the moving solubility target and the inventors' ignorance of the state of the art.

[281] Dr. Stella described many of the details of his experiments, and submitted the reports (several dozen) that he sent to the National Cancer Institute over the period of the project. Many different solutions were tried, but it does not appear that the testing of those solutions was particularly arduous or outside the routine.

(c) *Is there a motive provided in the prior art to find the solution the patent addresses?*

[282] Dr. Stella testified that he saw lyophilisation as something that should be tried in the course of their work. He considered lyophilisation to be one of the tools at his disposal to try to obtain a useful formulation, and he would be remiss not to try it. I infer that a skilled person would have had the same view.

[283] With regard to the bulking agent, there were a few options, but mannitol was one of the most popular, and it was obvious to try.

[284] Millennium argues that the skilled person would not have been motivated to try lyophilisation of bortezomib and mannitol because of the possibility that one or more esters would form. In my view, this possibility would not be sufficient to dissuade a skilled person.

That person would know that (i) an ester may not form, and (ii) any ester that did form would be expected to be readily reversible.

[285] Accordingly, it is my view that there was indeed a motive to try lyophilisation of bortezomib and mannitol.

(d) *Conclusion on Obviousness*

[286] As indicated in paragraph [83] above, the mere possibility that something might turn up is insufficient to establish that it was more or less self-evident to try to obtain the invention. On the other hand certainty is not required. Some amount of uncertainty is permissible in an obvious-to-try analysis.

[287] For the reasons set out above, it is my view that the solution provided by the 146 Patent, lyophilisation of bortezomib and mannitol, would have been obvious to try. It was obvious to try lyophilisation and, having decided to do so, it was obvious that a bulking agent would be needed. Moreover, it was obvious to try mannitol as the bulking agent.

[288] As with the 936 Patent, it is my view that the commercial success of Velcade cannot save the claims in issue of the 146 Patent from obviousness. Even though the bortezomib mannitol ester that is claimed in the 146 Patent was necessary to the success of Velcade, it was not sufficient. The evidence indicates that the improved properties of solubility and dissolution rate, which made an important contribution to Velcade being a practical commercial product, were the result of a large excess of mannitol in the formulation. The inventive concept of the claims in issue of the 146 Patent does not contemplate such an excess of mannitol. Accordingly, I

conclude that the inventive concept of the 146 Patent lacks the required causal link with the commercial success.

[289] Before concluding this section, I take this opportunity to make a few comments about the CAFC decision which upheld the validity of the US patent that corresponds to the 146 Patent. In particular, I wish to note a few important differences between the present case and that before the CAFC that reduce its persuasiveness in my eyes.

[290] First, the standard to be met to impeach a patent in the US appears to be different. In Canada, a party challenging the validity of a patent must prove its case on a balance of probabilities. Based on the CAFC decision, it appears that invalidity of a US patent must be proved by clear and convincing evidence. My understanding is that this is a higher standard than balance of probabilities: *Microsoft Corp v i4i Limited Partnership et al*, 564 US 91 (2011), 131 S Ct 2238.

[291] Another important difference between the present case and that before the CAFC is the knowledge of the skilled person as to whether an ester might form when bortezomib and mannitol are lyophilized. The CAFC decision is based on the skilled person being unaware of this possibility, whereas the parties are agreed in the present case that, regardless of whether the skilled person includes a medicinal chemist, that person would have been aware of the possibility that an ester would form.

[292] A third important difference concerns the characteristics of the skilled person. In the US, the skilled person seems to be a formulator without the input of a medicinal chemist. This

explains its conclusion that the skilled person would be unaware of the possibility of ester formation. It appears that there was never an argument that a medicinal chemist would be part of the team. As indicated above, Teva has made that argument in the present case, and I have accepted it.

[293] A fourth important difference concerns the prior art that was considered relevant. The CAFC stated that "[n]o reference shows or suggests ester formation at freeze-drying conditions". The CAFC also stated none of the cited prior art "proposes lyophilization in the presence of mannitol to produce a new compound". Teva argues that these two statements indicate that the CAFC did not consider the 887 Application as prior art, since the 887 Application describes lyophilisation and the formation of an ester complex of mannitol and a boronic acid (see paragraph [255] above). It is not surprising that the CAFC did not consider the 887 Application as prior art since it was published on October 5, 2000, years after the apparent claimed invention date of December 1997. It appears that the 887 Application is relevant prior art in the present case, but not in the US.

[294] These important differences give me reasons not to be persuaded by the reasoning and conclusions of the CAFC.

C. *706 Patent: Claim Construction*

[295] I preface this section by noting that I have not been directed to any court decision, either in Canada or outside, that has considered the 706 Patent or any corresponding foreign patent.

[296] As indicated in paragraph [63] above, claim construction is antecedent to consideration of both validity and infringement issues. Accordingly, this is where to start on the 706 Patent.

[297] As indicated in paragraph [61] above, the 706 Patent comprises five claims, of which claim 1 is the only independent claim. Claim 1 defines a detailed four-step process for the large-scale production of bortezomib or a boronic acid anhydride thereof. Claim 1 covers more than three pages and is reproduced in its entirety, along with the other claims of the 706 Patent, in the Annex at the end of this decision.

[298] For the purposes of claim construction, it will be helpful to deal individually with the preamble and each of the four steps of claim 1. The steps are identified as (aa), (bb), (cc) and (dd). In discussing claim construction, I will bear in mind the principle that "it is essential to see where the shoe pinches so that one can concentrate on the important points": *Shire Biochem Inc v Canada (Minister of Health)*, 2008 FC 538 at para 21; *Nokia v Interdigital Technology Corporation*, [2007] EWHC 3077 (UK Pat). Accordingly, I will focus my analysis on the aspects of the claims about which the parties disagree.

[299] Of course, in order to properly construe the claims of the 706 Patent, it is necessary to determine who the skilled person is to whom the patent is addressed.

(1) Person Skilled in the Art

[300] The parties agree that the skilled person to whom the 706 Patent is addressed would have a graduate level degree in synthetic organic chemistry and a few years of experience. There does

not appear to be any dispute that the skilled person should have some familiarity with boron chemistry.

[301] Millennium's expert Dr. Barrett opined that the skilled person should also have experience in process scale-up. Teva's expert Dr. Kabalka suggested that a chemist working in an industrial context will have large scale in mind even if s/he is not personally engaged in the process of scaling up. I agree. In my opinion, even though experience in a scale-up group may be helpful, it is not necessary for the skilled person.

(2) Large-scale

[302] The first area of disagreement between the parties regarding claim construction of the 706 Patent concerns the term "large-scale" in the preamble of claim 1.

[303] Certainly, this term is vague without some context. Therefore, it is permissible to have recourse to the disclosure of the 706 Patent in understanding this term. Fortunately, the disclosure provides some assistance. Paragraph 31 thereof states as follows: "As used herein, the term 'large-scale' refers to a reaction that utilizes at least about five moles of at least one starting material." Teva relies on this definition.

[304] Millennium argues that this is not the whole story. Millennium notes that the above-mentioned definition is immediately preceded by a sentence which refers to the preceding paragraph in the disclosure: "The ether solvent preferably is one that is suitable for routine use in large-scale production." Millennium notes that that preceding paragraph, as well as much of the 706 Patent, concerns a distinct invention that was included in the disclosure of the 706 Patent but

which was later claimed in a separate divisional patent application. This other invention concerned other steps in the manufacturing process which come before those claimed in the 706 Patent. Millennium argues that the reference to "starting material" should be understood to refer to the beginning of the broader process, not just the process claimed in the 706 Patent.

[305] Unfortunately, Millennium's argument in this respect is not supported by the evidence. Millennium cites the evidence of Dr. Barrett in which he discussed the construction of the term "large-scale". However, he did not state that the term "large-scale" should be construed to refer to starting material at the beginning of the broader process not claimed in the 706 Patent. I conclude that "starting material" refers to material at the start of the process that is claimed in the 706 Patent.

[306] Dr. Barrett did point out other passages in the 706 Patent that contribute to the meaning of the term "large-scale". For example, he cited the following passage from paragraph 8: "Notably, the processes described herein are suitable for batch production on a large, multi-kilogram scale that is limited only by the size of the available manufacturing capabilities." He also cited paragraph 25 which states as follows: "In essence, the scale of the reaction is limited only by the size of the available manufacturing capabilities." Dr. Barrett opined that the term "large-scale" should be construed to refer to the amount of material need to supply the market, and that this amount would be smaller in the case of a very potent active ingredient like bortezomib which has such a small effective dose.

[307] In my view, the passages cited above from paragraphs 8 and 25 of the 706 Patent do not detract from or alter the definition provided in paragraph 31. Those passages essentially serve to

emphasize that there is no specific upper limit to the scale contemplated in the 706 Patent. On the other hand, the definition in paragraph 31 provides a lower limit to the scale. That definition applies to the term “large-scale”.

(3) Step (aa)

[308] Step (aa) defines coupling two compounds to form a dipeptide using three steps, (i), (ii) and (iii). In step (i), the two compounds are coupled “in the presence of 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) and a tertiary amine in dichloromethane”. Step (ii) is “performing a solvent exchange to replace dichloromethane with ethyl acetate”. Step (iii) is “performing an aqueous wash of the ethyl acetate solution”.

[309] Millennium argues that the following elements of step (aa) are not essential:

1. Dichloromethane in step (i);
2. Replacing dichloromethane with ethyl acetate in step (ii); and
3. Ethyl acetate in step (iii).

[310] Millennium’s position on these points is based on the testimony of Dr. Barrett that, while dichloromethane and ethyl acetate are preferred, the skilled person would have known that other solvents could be used without changing the way the invention works.

[311] To determine whether a claim element is essential, I must turn to the passage from *Free World Trust* quoted in paragraph [70] above. To determine that an element is considered non-essential, the first question is whether, on a purposive construction of the words of the claim, it was clearly not intended to be essential.

[312] Step (aa) employs the terms “dichloromethane” and “ethyl acetate”. I have heard no argument that these terms are open to different meanings. I understand that they are clear and unambiguous, and I see no reason to conclude that the inventors intended that they should be construed to encompass compounds other than “dichloromethane” or “ethyl acetate” simply because the skilled person would have known of the possibility of using other solvents. In fact, the use of these terms when other options were known to be available suggests, in my opinion, that the inventors intended to limit the scope of step (aa) to these compounds.

[313] Further, step (ii) of step (aa) explicitly defines performing a solvent exchange. I see no reason to conclude that the inventors would have included this step in claim 1 if they viewed it as non-essential. Its inclusion suggests essentiality.

[314] I am unable to conclude that the words of the claim that Millennium argues are non-essential were clearly not intended to be essential. This is sufficient to conclude that the claim elements in issue are essential.

[315] Though it is not necessary to address the second question from *Free World Trust*, I do so here. That second question is whether, at the date of publication of the patent, the skilled addressees would have appreciated that a particular element could be substituted without affecting the working of the invention. To answer this question, I must consider whether a skilled worker, being told of both the element specified in the claim and the variant, would conclude that they would obviously work in the same way; that is to say that they would perform substantially the same function in substantially the same way to obtain substantially the same result.

[316] The variant provided by Teva's processes is not performing [redacted]. Teva details a number of differences in how the process works when a [redacted]. I need address only one. Dichloromethane is heavier than water, whereas ethyl acetate is lighter than water. Accordingly, when the aqueous layer (which contains impurities) is to be removed, it is on the top of the flask when dichloromethane is used, but on the bottom of the flask when ethyl acetate is used. Removal of the waste aqueous layer is simpler when it can simply be drained from the bottom of the flask. If the waste aqueous layer is at the top instead, then the desired solution must first be removed and set aside for later replacement in the flask after the aqueous layer has been removed. Both Dr. Bishop and Millennium's own documentation described this extra step as tedious.

[317] In my view, Teva's variant works in a substantially different way, and hence its use materially affects the working of the invention. This is another basis on which to conclude that the claim elements in step (aa) identified by Millennium are essential.

(4) Step (bb)

[318] Step (bb) defines removing a protecting group on the N-terminus from the compound made in step (aa). Step (bb) has three steps, (i), (ii) and (iii). Step (i) involves treating the compound with HCl in ethyl acetate. Step (ii) involves adding heptane. Step (iii) involves isolating by crystallization the resulting compound as its HCl addition salt.

[319] Millennium argues that the following are not essential:

1. Ethyl acetate in step (i);
2. Heptane in step (ii); and
3. The acid addition salt in step (iii).

[320] Just as in respect of step (aa), Millennium's position on these points is based on the assertion that the skilled person would have known of alternatives that could be used without changing the way the invention works. As with step (aa), I can decide the issue of essentiality based on whether the skilled reader would have understood from the language of the claim that the patentee intended that strict compliance with the primary meaning was an essential requirement of the invention. As in step (aa), I see no ambiguity in the terms used in step (bb) that would lead to a conclusion that they encompass a range of alternatives. Step (bb) explicitly calls for ethyl acetate, heptane and the HCl addition salt. Dr. Barrett opined that "heptane" could contemplate various isomers other than n-heptane. It would not be fruitful to explore this view because there is no allegation that Teva's processes used any such isomers. [redacted]

[321] In my view, the elements asserted by Millennium are essential.

(5) Step (cc)

[322] Step (cc) defines coupling the compound resulting from step (bb) with a reagent to introduce a pyrazine carbonyl N-terminal protecting group using the same three steps as defined in step (aa): (i) coupling in the presence of TBTU and a tertiary amine in dichloromethane, (ii) performing a solvent exchange to replace dichloromethane with ethyl acetate, and (iii) performing an aqueous wash of the ethyl acetate solution.

[323] Millennium makes the same assertions of non-essentiality in respect of step (cc) as it does in respect of step (aa). I reach the same conclusions here as I did there.

[324] In my view, the elements asserted by Millennium are essential.

(6) Step (dd)

[325] Step (dd) defines deprotecting the boronic acid moiety on the compound resulting from step (cc) using four steps, (i), (ii), (iii) and (iv). Step (i) involves providing a biphasic mixture of that compound, an organic acid receptor, a lower alkanol, a C_{5-8} hydrocarbon solvent, and aqueous mineral acid. Step (ii) involves stirring the mixture to afford bortezomib. Step (iii) involves separating the solvent layers. Step (iv) involves extracting bortezomib or a boronic acid anhydride thereof into an organic solvent.

[326] Millennium makes no assertion of non-essentiality in respect of any part of step (dd). Therefore, all elements of step (dd) are considered essential.

(7) Claim 2

[327] Claim 2 is dependent on claim 1 and defines the reagent of step (cc) as 2-pyrazine carboxylic acid.

[328] Millennium makes no assertion of non-essentiality in respect of claim 2. Therefore, 2-pyrazine carboxylic acid is essential to claim 2.

(8) Claim 3

[329] Claim 3 is dependent on claim 2 and defines four steps within step (dd)(iii) of claim 1 (separating the solvent layers). These steps are (1) separating the solvent layers, (2) adjusting the aqueous layer to basic pH, (3) washing the aqueous layer with an organic solvent, and (4) adjusting the aqueous layer to a pH less than 8.

[330] Millennium makes no assertion of non-essentiality in respect of claim 3. Therefore, all of the steps defined in claim 3 are essential thereto.

(9) Claim 4

[331] Claim 4 is dependent on claim 3 and specifies that the compound referred to in step (dd)(iv) of claim 1 is extracted into dichloromethane, the solvent is exchanged to ethyl acetate, and the compound is crystallized by addition of hexane or heptane.

[332] Much as in steps (aa), (bb) and (cc) in claim 1, Millennium argues that certain elements added in claim 4 are not essential. Specifically, similar to claim 1, Dr. Barrett opined that the replacement of dichloromethane by ethyl acetate and the use of hexane or heptane in crystallization are not essential because the skilled person would have known of alternatives that could be used without changing the way the invention works. It also argues that n-heptane is not essential.

[333] I have the same view here as previously expressed. The terms in question are clear and unambiguous, and I see no reason to construe them to encompass other compounds or to read them out. The elements in question are essential.

(10) Claim 5

[334] Claim 5 is dependent on claim 3 and specifies that the boronic acid anhydride resulting from step (dd) of claim 1 is boroxine, and that said boroxine is (just as in claim 4) extracted into dichloromethane, the solvent is exchanged to ethyl acetate, and the compound is crystallized by addition of hexane or heptane.

[335] Millennium makes the same arguments of non-essentiality of elements in claim 5 as in claim 4. My conclusion is the same: all elements of the claim 5 are essential thereto.

D. *706 Patent: Infringement by Teva-bortezomib*

[336] There is no dispute concerning the steps taken in the process of manufacturing Teva-bortezomib. Millennium accepts that, in order to make its case that the manufacture of Teva-bortezomib infringes the 706 Patent, it must be successful on its construction of "large-scale" and on its assertions of non-essentiality of various claim elements. As indicated in the previous section, Millennium has been entirely unsuccessful in this regard. With regard to "large-scale", Millennium does not assert that [redacted] of any material is used at the start of step (aa) of the process for manufacturing Teva-bortezomib as contemplated in claim 1. In addition, Millennium does not assert that the process for manufacturing Teva-bortezomib incorporates all of the elements of claim 1 that it argues are non-essential.

[337] It follows therefore that the process for manufacturing Teva-bortezomib does not infringe claim 1 of the 706 Patent. Because all of claims 2-5 are dependent on claim 1, it also follows that none of these claims is infringed.

E. *706 Patent: Infringement by Act-bortezomib*

[338] As with the Teva-bortezomib manufacturing process, there is no dispute concerning the steps taken in the process of manufacturing Act-bortezomib. An important difference between the Act-bortezomib manufacturing process and the Teva-bortezomib manufacturing process is that [redacted] Relying on the opinion of its expert Dr. Barrett, Millennium argues that the Act-bortezomib manufacturing process is therefore a large-scale process even if the definition in paragraph 31 of the 706 Patent is considered limitative.

[339] Teva notes that the definition in paragraph 31 of the 706 Patent refers to a reaction that utilizes at least about five moles of at least one starting material. [redacted] Teva's expert Dr. Kabalka opined that this [redacted] cannot be considered in determining whether a reaction is large-scale because the 706 Patent explains that one advantage of the patented process is to avoid the inefficient repetition of small-scale processes.

[340] In his reply expert report, Dr. Barrett did not respond to this aspect of Dr. Kabalka's opinion other than to state that his opinion was unchanged.

[341] I agree with Dr. Kabalka's reasoning and I adopt his opinion that the Act-bortezomib manufacturing process is not a large-scale process.

[342] Even if I am wrong about whether the Act-bortezomib manufacturing process is a large-scale process, I conclude nevertheless that it does not infringe the claims of the 706 Patent because, like the Teva-bortezomib manufacturing process, it does not incorporate all of the elements of claim 1 that Millennium argues are non-essential, but which actually are essential.

F. *706 Patent: Obviousness*

[343] As discussed in the previous section, my infringement analysis has concluded that Teva's allegedly infringing processes are missing several essential elements of the claims of the 706 Patent, and therefore do not infringe. It follows from this that the counterclaim in this action will be dismissed. Since Teva's allegation of obviousness of the 706 Patent is in defence against the counterclaim, it is not necessary for me to reach a conclusion on obviousness. Accordingly, I will not analyze this issue.

VII. Conclusion

[344] In the Analysis section above, I have concluded that:

1. The claims in issue of the 936 Patent are invalid for obviousness;
2. The claims in issue of the 146 Patent are invalid for obviousness; and

3. The processes to manufacture Teva-bortezomib and Act-bortezomib do not infringe the 706 Patent.

[345] It follows that Teva has been successful in making its case for compensation under s. 8 of the *Regulations*, and that Millennium and the other plaintiffs by counterclaim have been unsuccessful in their counterclaim seeking various remedies (including damages) for alleged infringement of the 936, 146 and 706 Patents.

[346] I understand that the parties have agreed that the amount of compensation to which Teva is entitled is as stated in the Minutes of Partial Settlement they executed on December 20, 2017. In my view, it is not necessary for my Judgment to address the amount of compensation because there is no disagreement on this issue.

[347] I want to take this opportunity before concluding to thank the parties for settling several issues and for focussing on the real issues in dispute. I also want to thank counsel for cooperating in the efficient introduction of evidence which ensured that the trial of this action proceeded smoothly and was completed earlier than anticipated.

[348] Teva should have its costs. If the parties are unable to agree on the quantum of costs, I will receive submissions from the parties as contemplated in the Judgment below.

JUDGMENT in T-944-15

THIS COURT'S JUDGMENT is that:

1. The action for compensation under s. 8 of the *Patented Medicines (Notice of Compliance) Regulations* is granted.

2. The counterclaim is dismissed.

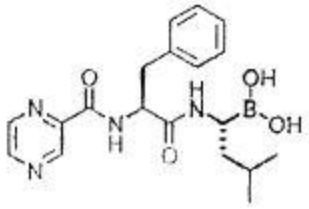
3. Costs will follow the event. If the parties are unable to agree on the quantum of costs, the plaintiff shall serve and file its costs submissions, of no more than 12 pages, within 30 days following the date of this decision. The defendants and plaintiffs by counterclaim shall have 15 days following receipt of the plaintiff's submissions to serve and file their responding costs submissions which shall be limited to 15 pages. Thereafter, the plaintiff may, within five (5) days following receipt of responding submissions, serve and file reply costs submissions of no more than three (3) pages.

"George R. Locke"
Judge

ANNEX

WHAT IS CLAIMED IS:

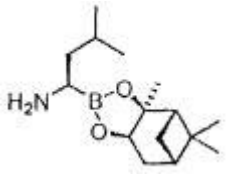
1. A large-scale process for forming a compound of formula (***XIV***);



(***XIV***)

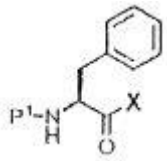
or a boronic acid anhydride thereof comprising the steps:

(aa) coupling a compound of formula (***XVIII***):



(***XVIII***)

or an acid addition salt thereof, with a compound of formula (***XIX***):



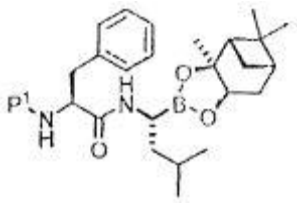
(***XIX***)

wherein:

P^1 is a cleavable amino group protecting moiety; and

X is OH or a leaving group;

to form a compound of formula (***XX***):



(***XX***)

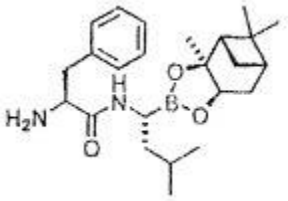
wherein P^1 is as defined above, said coupling step (aa) comprising the steps;

(i) coupling the compound of formula (***XVIII***) with a compound of formula (***XIX***) wherein X is OH or a leaving group, in the presence of 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) and a tertiary amine in dichloromethane;

(ii) performing a solvent exchange to replace dichloromethane with ethyl acetate; and

(iii) performing an aqueous wash of the ethyl acetate solution;

(bb) removing the protecting group P^1 to form a compound of formula (***XXI***):



(***XXI***)

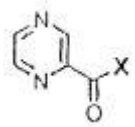
or an acid addition salt thereof, said protecting group removing step (bb) comprising the steps:

(i) treating the compound of formula (***XX***) with HCl in ethyl acetate;

(ii) adding heptane to the reaction mixture; and

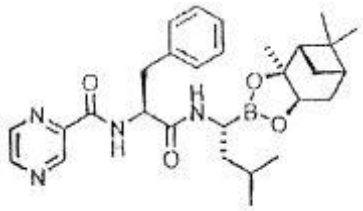
(iii) isolating by crystallization the compound of formula (***XXI***) as its HCl addition salt;

(cc) coupling the compound of formula (***XXI***) with a reagent of formula (***XXII***)



(***XXII***)

wherein X is OH or a leaving group, to form a compound of formula (***XXIII***):



(***XXIII***)

said coupling step (cc) comprising the steps:

(i) coupling the compound of formula (XXI) with the reagent of formula (XXII) in the presence of TBTU and a tertiary amine in dichloromethane;

(ii) performing a solvent exchange to replace dichloromethane with ethyl acetate; and

(iii) performing an aqueous wash of the ethyl acetate solution; and

(dd) deprotecting the boronic acid moiety to form the compound of formula (***XIV***) or a boronic acid anhydride thereof, said deprotecting step (dd) comprising the steps:

(i) providing a biphasic mixture comprising the compound of formula (***XXIII***), an organic boronic acid acceptor, a lower alkanol, a C_{5-8} hydrocarbon solvent, and aqueous mineral acid;

(ii) stirring the biphasic mixture to afford the compound of formula (***XIV***);

(iii) separating the solvent layers; and

(iv) extracting the compound of formula (XIV), or a boronic acid anhydride thereof, into an organic solvent.

2. The process of claim 1, wherein the reagent (***XXII***) is 2-pyrazine-carboxylic acid.

3. The process of claim 2, wherein step (dd)(iii) comprises the steps:

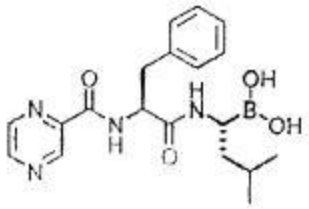
(1) separating the solvent layers;

(2) adjusting the aqueous layer to basic pH;

(3) washing the aqueous layer with an organic solvent; and

(4) adjusting the aqueous layer to a pH less than 8.

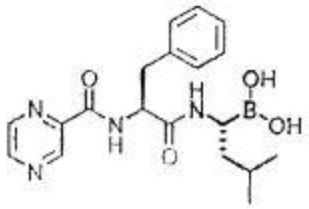
4. The process of claim 3, wherein in step (dd)(iv), the compound of formula (***XIV***):



(***XIV***)

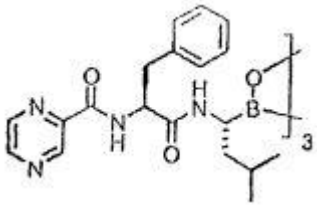
or a boronic acid anhydride thereof, is extracted into dichloromethane, the solvent is exchanged to ethyl acetate, and the compound of formula (***XIV***), or a boronic acid anyhydride thereof, is crystallized by addition of hexane or heptane.

5. The process of claim 3, wherein the step (dd)(iv) the boronic acid anhydride of the compound of formula (***XIV***):



(***XIV***)

is a cyclic trimeric boronic acid anhydride of formula (***XXIV***):



(***XXIV***)

and wherein the cyclic trimeric boronic acid anhydride of formula (***XXIV***) is extracted into dichloromethane, the solvent is exchanged to ethyl acetate, and then the cyclic trimeric boronic acid anhydride of formula (***XXIV***) is crystallized by addition of hexane or heptane.

FEDERAL COURT

SOLICITORS OF RECORD

DOCKET:	T-944-15
STYLE OF CAUSE:	TEVA CANADA LIMITED v JANSSEN INC. AND MILLENNIUM PHARMACEUTICALS, INC. AND MILLENNIUM PHARMACEUTICALS INC., JANSSEN INC., CILAG GMBH INTERNATIONAL, CILAG AG AND JANSSEN PHARMACEUTICA NV v THE UNITED STATES OF AMERICA REPRESENTED BY THE DEPARTMENT OF HEALTH AND HUMAN SERVICES AND TEVA CANADA LIMITED
PLACE OF HEARING:	OTTAWA, ONTARIO
DATE OF HEARING:	JANUARY 30-31, 2018 FEBRUARY 6-28, 2018 MARCH 1-9, 2018
PUBLIC JUDGMENT AND REASONS:	LOCKE J.
DATED:	JULY 18, 2018

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Borden Ladner Gervais LLP Barristers and Solicitors Ottawa, Ontario AND Lenczner Slaght Royce Smith Griffin LLP Barristers and Solicitors Toronto, Ontario	FOR THE DEFENDANTS/ PLAINTIFFS BY COUNTERCLAIM JANSSEN INC., CILAG GMBH INTERNATIONAL, CILAG AG AND JANSSEN PHARMACEUTICA NV
Gowling WLG (Canada) LLP Barristers and Solicitors Ottawa, Ontario	PATENTEE ADDED PURSUANT TO S. 55(3) OF THE *PATENT ACT*