Federal Court  Cour fédérale

Date: 20191029

Docket: T-1661-17

Citation: 2019 FC 1355

BETWEEN:

JANSSEN INC. and
JANSSEN ONCOLOGY, INC.,
BTG INTERNATIONAL LTD.

Applicants

and

APOTEX INC. and
THE MINISTER OF HEALTH

Respondents

REASONS FOR JUDGMENT

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PHELAN J.

I. INTRODUCTION

[1] This is an application brought under subsection 55.2(4) of the *Patent Act*, RSC 1985, c P-4 [Act] and subsection 6(1) of the *Patented Medicines (Notice of Compliance) Regulations*, SOR/93-133, as they appeared on September 20, 2017 [Regulations], to prohibit the Minister of Health from issuing a Notice of Compliance to Apotex Inc [Apotex].

[2] The Regulations prior to amendment in 2017 apply because the Respondent, Apotex, served its Notice of Allegation [NOA] on the Applicant, Janssen Inc [Janssen], on September 19, 2017, two days before the new Regulations came into force on September 21, 2017. According to the transition provisions in subsection 9(1) of the *Regulations Amending the Patented Medicines (Notice of Compliance) Regulations, 2017*, SOR/2017-166, the old Regulations continue to apply for a matter relating to a notice of allegation served on the first person before the amendments came into force.

[3] The nub of the dispute is the function of prednisone [PN] as an anti-cancer agent and/or as a means to treat the side effects caused by abiraterone acetate [AA].

[4] The Applicants [collectively, "Janssen"] state that Canadian Patent No. 2,661,422 [422 Patent or the Patent] claims the invention of the combination of AA and PN for the treatment of prostate cancer, meaning that both compounds work in combination to have an anti-cancer effect. The Respondent, Apotex, asserts that Janssen is merely combining two elements that were known to have separate anti-cancer effects and do not work synergistically. Apotex also claims that both Janssen's and Apotex's AA drug products are not proposed for the same use as that claimed by the 422 Patent because the Apotex drug products indicate AA as the anti-cancer treatment with PN prescribed only to treat adverse side effects.

[5] A significant problem in this case is that the anti-cancer role of PN that is claimed in the 422 Patent when used in combination with AA appears to no longer be understood as the main role PN plays in cancer treatment. Instead, PN is now primarily understood to address the side

effects caused by AA. The interpretation of how the combination is claimed in the 422 Patent – the claim construction – significantly impacts the Court's findings.

[6] The relief sought is an order to the Minister of Health prohibiting the issuance of a Notice of Compliance [NOC] to Apotex for its drug APO-ABIRATERONE. Other relief in the nature of declaration was abandoned.

II. BACKGROUND

A. *Procedural History*

[7] Cougar Biotechnology Inc, [Cougar] filed an application for Canadian Patent 2,661,422 on August 23, 2007, which was published on February 28, 2008, and issued on June 27, 2017. Its priority filing date based on a US Patent was August 25, 2006. Cougar was renamed Janssen Oncology Inc (one of the Applicants) in 2012. The 422 Patent is listed by Janssen Inc on the Patent Register for Janssen's AA product, which has the brand name ZYTIGA. The first Notice of Compliance for ZYTIGA appears to have been issued on July 27, 2011. The 422 Patent was listed on the Patent Register for ZYTIGA when the patent was issued on June 27, 2017.

[8] On July 28, 2017, Apotex filed an Abbreviated New Drug Submission with the Minister of Health seeking a Notice of Compliance for APO-ABIRATERONE (250 mg oral tablets containing AA), using ZYTIGA as the Canadian reference product.

[9] On September 18, 2017, Apotex sent its NOA to Janssen alleging that the 422 Patent is invalid, would not be infringed by APO-ABIRATERONE, and is ineligible to be listed on the register. The NOA was received by Janssen on September 19, 2017.

[10] The new Regulations came into effect on September 21, 2017.

[11] Janssen filed its Notice of Application in this Court on November 1, 2017. Therefore, the "deadline date" for a decision if the Court is to prohibit issuing Apotex an NOC is November 1, 2019.

B. *Facts*

(1) The Witnesses

[12] Janssen's fact witnesses are:

- Dr. Ian Judson, a physician and former researcher involved in the development of AA monotherapy. He described the initial research and the publication of the O'Donnell 2004 article, an important piece of prior art in this case.
- Dr. Johann de Bono who, while not the inventor, believes that he contributed to the invention of the Patent. He is a physician focussing on prostate cancer research.
- Dr. Gloria Lee, a physician and former Vice President of Clinical Research and Development at Cougar, which sponsored the clinical trials leading to the invention claimed in the 422 Patent.

- Dr. Robert Charnas, Global Regulatory Leader at Cougar who was responsible for the AA and PN project starting in 2008.

[13] Janssen's expert witnesses are:

- Dr. Matthew Rettig (medical oncologist).
- Dr. Richard Auchus (endocrinologist).
- Dr. Alan So (urologist).
- Dr. Jan Sedgeworth (regulatory affairs consultant).

[14] Apotex's expert witnesses are Dr. Robert Nam (uro-oncologist) and Dr. Gail Prins (endocrinologist). Important aspects of their expert reports are referred to in these reasons.

(2) Scientific Background

[15] The general scientific background that the experts agree on and that will aid in understanding the case is set out in the following paragraphs. This information forms part of the common general knowledge as of the Filing Date and the Publication Date.

(a) *Prostate Cancer Treatment*

[16] Prostate cancer is the most commonly diagnosed cancer in men and is the third leading cause of all cancer-related death in men in Canada. Prostate cancer results from the uncontrolled growth of cells in the prostate gland. In its early stages, prostate cancer is confined to the prostate

gland. Early stage cancer might be left untreated and monitored by active surveillance. If prostate cancer spreads to other parts of the body, it is called metastatic prostate cancer.

[17] Male sex hormones (androgens), specifically testosterone, have long been known to promote prostate cancer. Therefore, the primary treatment for metastatic prostate cancer has been androgen deprivation therapy [ADT] through medical or surgical castration to suppress androgen production in the testes. Patients treated with ADT still have some residual androgens in their system because the adrenal gland produces about 10% of a man's androgens. After some time, on average between 12 to 33 months, patients treated with ADT have their prostate cancer begin to progress again. When prostate cancer progresses after being treated with ADT, it is called castrate resistant prostate cancer [CRPC]; if it is also metastatic cancer, it is referred to as mCRPC. In earlier publications, CRPC was also referred to as "hormone refractory prostate cancer" or "androgen independent prostate cancer", among other variations.

[18] As of 2007, what caused prostate cancer to become castration resistant was not fully known. Whether residual androgens from the adrenal gland were thought to play a significant role in mCRPC is a major point of disagreement between the experts.

[19] Prostate specific antigen [PSA], a protein produced by the prostate gland, was measured to both initially detect prostate cancer and to indicate the response of prostate cancer to treatments in 2007. PSA response was used as a surrogate measurement for the effectiveness of prostate cancer treatments, although it was not perfectly correlated with other indicators of treatment success, like survival benefit. A significant PSA response in 2007 was defined as a

decline in PSA levels by 50% or more confirmed by a second PSA measurement four weeks later.

[20] As of 2007, a new type of chemotherapy drugs called taxanes, and specifically docetaxel, had been shown to provide a modest survival benefit for patients with mCRPC. Docetaxel, however, had significant toxicity and side effects.

(b) *Clinical Trials*

[21] There are three types of clinical trials for cancer treatments. Phase I trials are small and short in duration; they are meant to determine safety and dosage of the drug. Phase II trials examine efficacy and side effects of the drug and would include several hundred patients studied over a few months to a few years. Phase III trials would have 300 to 3,000 patients and are designed to examine the drug's safety, effectiveness, and an acceptable balance of costs and benefits.

(c) *Steroid Hormone Synthesis*

[22] Janssen's expert, Auchus, provided a helpful overview of steroid hormone synthesis. Steroid hormones regulate a variety of processes in the body based on the receptor to which they bind. All steroid hormones are synthesized from cholesterol. There are three types of steroid hormones: mineralocorticoids, glucocorticoids, and sex steroids. Given their similar structure and overlapping synthesis pathways, the divisions between the categories of steroid hormones are not always absolute, as some steroids may have multiple overlapping functions. Steroid

synthesis is complex. Steroid synthesis requires enzymes along each step of the synthesis pathways.

[23] In men, the testes produce sex steroids, or androgens, which are mainly testosterone, dihydrotesterone, dehydroepiandrosterone, and androstenedione. The testes produce most of a man's testosterone.

[24] The adrenal gland also produces some androgens, as well as glucocorticoids and mineralocorticoids. Glucocorticoids are necessary for the body to respond to stress. The major glucocorticoid is cortisol. Corticosterone is the secondary glucocorticoid in humans. Mineralocorticoids, primarily aldosterone, regulate water and salt retention.

[25] Inhibiting an enzyme along the steroid synthesis pathway could affect several of the steroids downstream. The cholesterol side chain cleavage enzyme or desmolase, is necessary for the production of all adrenal steroids. Inhibiting desmolase would suppress all adrenal steroids.

[26] The 17α-hydroxylase/ $C_{17,20}$-lyase [CYP17] enzyme has two activities in adrenal steroid synthesis: 17α-hydroxylase activity and 17,20-lyase activity. 17α-hydroxylase activity is necessary for the production of cortisol as well as androgens. 17,20-lyase activity only affects the production of androgens.

[27] The hormone, adrenocorticotropic hormone [ACTH], controlled by the hypothalamus and pituitary gland regulates the secretion of glucocorticoids and androgens from the adrenal gland.

Mineralocorticoids are affected by the renin-angiotensin II-aldosterone system as well as by ACTH.

[28] When the adrenal gland's ability to produce glucocorticoids and mineralocorticoids is impaired or when the body does not produce enough ACTH, this can result in a condition called adrenal insufficiency. Symptoms of adrenal insufficiency include low blood pressure, fatigue, anorexia, weight loss, abdominal pain, low blood sugar, low sodium, and hyperpigmentation. Adrenal crisis is a potential life-threatening condition when the body cannot produce enough steroids to respond to a serious stressor. Mineralocorticoid excess occurs when mineralocorticoids are overproduced causing symptoms such as high blood pressure, low potassium and fluid retention. Adrenal function can be tested using a Synacthen test which creates an artificial stress response to test whether cortisol levels respond to stress appropriately.

[29] Artificial glucocorticoids such as hydrocortisone, PN, and dexamethasone can be used to treat adrenal insufficiency and mineralocorticoid excess, which is called glucocorticoid replacement therapy. Glucocorticoid replacement theory has some risks and side effects. However, the experts differed as to whether glucocorticoid replacement therapy using artificial glucocorticoids would be preferred over other options.

(3) The 422 Patent and Asserted Claims

[30] The 422 Patent disclosure describes the field of the invention as being methods for treating cancer by administering a CYP17 enzyme inhibitor such as AA "in combination with at least one additional therapeutic agent, such as an anti-cancer agent or a steroid." The Patent

discloses a number of potential therapeutic agents including cytotoxic chemotherapy drugs and glucocorticoids for potential use in combination with a CYP17 enzyme inhibitor. One embodiment described is an amount of about 50 to 2000 mg per day of AA and an amount of about 0.01 to 500 mg per day of glucocorticoid including hydrocortisone, PN or dexamethasone.

[31] The range of PN covered by the Patent is significantly large. It would include the amounts Apotex proposes to be used for the treatment of side effects. Apotex's amounts are at the low end (10 mg) of Janssen's range.

[32] The 422 Patent disclosure defines several terms, including:

> …the terms "treat", "treating" and "treatment" include the eradication, removal, modification, management or control of a tumor or primary, regional, or metastatic cancer cells or tissue and the minimization or delay of the spread of cancer
>
> …the phrase "therapeutically effective amount" when used in connection with a 17α-hydroxylase/ $C_{17,20}$-lyase inhibitor or therapeutic agent means an amount of the 17α-hydroxylase/ $C_{17,20}$-lyase inhibitor or therapeutic agent effective for treating a disease or disorder disclosed herein, such as cancer.
>
> …the phrase "refractory cancer," means cancer that is not responding to an anti-cancer treatment or cancer that is not responding sufficiently to an anti-cancer treatment. Refractory cancer can also include recurring or relapsing cancer.

[33] The 422 Patent disclosure cites three US Patents, including the US Patent 5,604,213 dated February 18, 1997 [213 Patent], for the method of making AA and other CYP17 inhibitors. It cites the 213 Patent as supporting the use of CYP17 inhibitors in the treatment of prostate cancer.

[34] The disclosure describes the amount of glucocorticoid to be used with a CYP17 inhibitor as "an amount that is sufficient to treat the cancer whether administered alone or in combination with a 17α-hydroxylase/ $C_{17,20}$-lyase inhibitor." The amount of CYP17 inhibitor is also described as being the amount sufficient to treat the cancer whether administered alone or in combination with an additional anti-cancer treatment.

[35] The 422 Patent disclosure describes the CYP17 inhibitor and the additional therapeutic agent as being able to be administered in separate compositions or in a single composition.

[36] The 422 Patent describes that a suitable daily dosage of the CYP17 inhibitor depends on a number of factors including the severity of the condition, the particular inhibitor, the method of administration, and the age, weight and response of the patient. Suitable dosages are given as generally ranging from 0.0001 to 1000 mg/kg/day. For treating cancer with a combination of a CYP17 inhibitor and PN, the recommended dosage range is 50 to 2000 mg per day of AA and 0.01 to 500 mg per day of PN or 500 to 1500 mg per day of AA and 10 to 250 mg per day of PN.

[37] The claims at issue in these proceedings are claims 3, 6, 7, 14, and 15 [Asserted Claims]. The Asserted Claims are all directed towards the use of a therapeutically effective amount of AA and a therapeutically effective amount of PN to treat prostate cancer, refractory prostate cancer, and refractory prostate cancer that is resistant to one or more anti-cancer agents.

[38] These Asserted Claims, which refer to the definitions earlier outlined, read as follows:

> 3. Use of a therapeutically effective amount of abiraterone acetate or a pharmaceutically acceptable salt thereof and a

> therapeutically effective amount of prednisone, for the treatment of a prostate cancer in a human.
>
> 6. The use according to any one of claims 1-3, wherein the therapeutically effective amount of the abiraterone acetate or pharmaceutically acceptable salt thereof is 1000 mg/day.
>
> 7. The use according to any one of claims 1-3, wherein the therapeutically effective amount of the abiraterone acetate or a pharmaceutically acceptable salt thereof is in at least one oral dosage form comprising about 250 mg of abiraterone acetate or a pharmaceutically acceptable salt thereof.
>
> 14. Use of a therapeutically effective amount of abiraterone acetate or a pharmaceutically acceptable salt thereof, and a therapeutically effective amount of prednisone for the treatment of a refractory prostate cancer in a human.
>
> 15. The use according to any one of claims 12-14, wherein the refractory prostate cancer is not responding to at least one anti-cancer agent.

(4) The Cougar Trials

[39] In 2004 Cougar received a licence to develop and commercialize AA. The first of Cougar's clinical trials of AA began in December 2005.

[40] The first trial (COU-AA-001) was led by de Bono. It was designed to evaluate AA therapy for men with mCRPC who had not had chemotherapy treatment. De Bono's hypothesis was that adding a glucocosticoid like PN or dexamethasone could reduce production of the upstream precursor adrenal steroids, reverse resistance to AA and therefore have an anti-cancer activity.

[41] The results of the study were that the single patient studied had a positive turnover response when given AA and dexamethasone. The results were presented at the Prostate Cancer Foundation Scientific Retreat on October 11, 2007, and published in Attard 2008 – Journal of Clinical Oncology on October 1, 2008.

[42] The Clinical Study Report completed in 2010 concluded that patients receiving AA then AA and dexamethasone in combination had approximately three months longer for PSA progression. De Bono described the results as "surprising and unexpected".

[43] A further Phase II study (COU-AA-004) began in June 2007. It was intended to evaluate the combination of AA and PN to treat patients with mCRPC. It confirmed the effectiveness of this combination treatment.

[44] The final study results were reported in Danila 2010 in the Journal of Clinical Oncology. In Danila 2010, the authors referenced that previous work had indicated that low-dose steroids could reverse clinical resistance to AA and decrease steroid precursors upstream of CYP17. In later Phase III studies, the combination of AA and PN demonstrated an unexpected survival benefit in patients, which was the first non-cytotoxic secondary hormonal therapy to show survival benefit. These results were published between 2011 and 2015.

(5) APO-ABIRATERONE and ZYTIGA

[45] ZYTIGA is Janssen's AA product, which comes in 250 mg uncoated and 500 mg coated oral tablets. In the first sentence of its Product Monograph under the Indications and Clinical Use

section, ZYTIGA is "indicated in combination with prednisone for the treatment of metastatic prostate cancer (castration resistant prostate cancer)…". The recommended daily dosage is 1000 mg of ZYTIGA with 10 mg of PN. The action and clinical pharmacology of AA, but not PN, is explained under the Action and Clinical Pharmacology section.

[46] In the Warnings and Precautions section, glucocorticoids are described as helping to prevent mineralocorticoid excess and adrenal insufficiency that may result from the administration of AA. The Consumer Information part of the ZYTIGA Product Monograph states that ZYTIGA in combination with PN is used to treat metastatic prostate cancer. It describes how ZYTIGA works to stop androgen production. The only explanation of how PN works in the Consumer Information section is under the "Proper Use of this Medication" section where it explains that PN is taken with ZYTIGA to help manage potential side effects.

[47] The ZYTIGA Product Monograph cites the following studies that examined the combination of AA with glucocorticoids:

1. Attard 2008: The study concluded that the combination of corticosteroids with AA prevents mineralocorticoid excess and "may maximize efficacy".

2. Attard 2009: This article concluded that the combination of AA with low-dose corticosteroids could maximize efficacy and minimize toxicity.

3. Ryan 2010: This article concluded that the impact of concurrent PN on response to treatment or long-term toxicity was not known.

4. Attard 2010 is a letter to the editor in response to the Ryan 2010 article. It reports that studies suggested that concomitant use of glucocorticoids with AA could result in a longer term tumour response than AA alone.

5. Danila 2010 reported the final results of COU-AA-004. The study concluded that AA and PN were well tolerated together with encouraging anti-tumour activity. The conclusion of the study focussed on the benefits of PN in reducing mineralocorticoid excess.

6. De Bono 2011 reported the Phase III trial COU-AA-301, which found that the combination of AA and PN resulted in a survival benefit for patients with mCRPC. The study did not discuss whether PN also had an anti-cancer effect; it focussed on the role of PN in reducing mineralocorticoid excess.

7. Ryan 2013 reported the interim results of the Phase III trial COU-AA-302, which showed the survival benefit from the combination of AA and PN. The study noted in the conclusion that PN also had anti-tumour activity

[48] APO-ABIRATERONE is Apotex's proposed AA product, which comes in 250 mg uncoated tablets. Similar to the ZYTIGA Product Monograph, APO-ABIRATERONE is "indicated in combination with prednisone for the treatment of metastatic prostate cancer (castration-resistant prostate cancer) in patients…". The recommended daily dosage is 1000 mg of APO-ABIRATERONE with 10 mg of prednisone. The mechanism of action for AA as a CYP17 inhibitor is described. No anti-cancer effects of PN are described.

[49] The Consumer Information section of the APO-ABIRATERONE Product Monograph contains essentially the same information as the ZYTIGA Product Monograph. APO-ABIRATERONE is described as being used in combination with PN to treat metastatic prostate cancer. It describes what AA does to suppress androgen levels, but does not describe PN as having an anti-cancer effect. PN is described as being a medication taken with AA to help manage potential side effects under the "Proper Use of this Medication" section.

[50] The APO-ABIRATERONE Product Monograph cites the ZYTIGA Product Monograph as well as the same studies cited in the ZYTIGA Product Monograph.

III. ISSUES

[51] The issues to be addressed in this decision are:

1. The acceptance and weight of the parties' expert evidence;
2. The burden of proof of Apotex's allegation of invalidity of the 422 Patent;
3. Claim construction including the appropriate persons of ordinary skill in the art, the applicable common general knowledge and the proper claim construction;
4. The validity of the 422 Patent as non patentable subject matter;
5. The obviousness of the 422 Patent;
6. The non utility of the Patent (Apotex's assertion of insufficiency and overbreadth has been discontinued as referenced in its written submissions);
7. The infringement of the 422 Patent; and
8. The eligibility of the 422 Patent to ground a prohibition order.

IV. ANALYSIS

A. *Expert Evidence*

[52] The first issue under this heading is Janssen's assertion that while each of the other experts could assist the Court, Prins, Apotex's expert endocrinologist, cannot. Unlike Apotex which contends that the Person of Ordinary Skill in the Art [POS] would not include an endocrinologist, Janssen put forward Auchus' evidence as part of its argument that an endocrinologist would be part of the POS.

[53] Janssen's objection to Prins is that she gave conflicting evidence on questions of primary importance regarding the impacts of congenital CYP17 deficiency on aldosterone levels and that she does not have any special knowledge to help the Court.

[54] Consistent with the Supreme Court's teachings in *R v J-LJ*, 2000 SCC 51 at para 56, [2000] 2 SCR 600, and *R v Mohan*, [1994] 2 SCR 9 at p 24, 114 DLR (4th) 419, the Court cannot accept an expert's conclusions without making its own independent assessment of the evidence – aided by the expert evidence. Each of the experts has provided the Court with useful evidence. The Court must weigh and consider the opinions on each of the issues separately.

[55] There is no reason not to admit Prins' evidence. While some of her evidence was inconsistent or confusing, those matters go to credibility and weight not to admissibility. Otherwise she is qualified to give evidence on endocrinology of prostate cancer treatments. Her qualifications as a PhD rather than a medical doctor do not render her incapable of giving expert evidence.

Her evidence may suggest that the invention was not as obvious as Apotex contends.

[56] The more important issue is whether endocrinology is relevant to this matter and whether a POS would include an endocrinologist. That issue is discussed later but I have concluded that an endocrinologist is not part of a POS.

[57] The second issue under this heading is the significance of the fact that Apotex's experts were "blinded" – they did not know the invention when giving evidence on "the state of the art" and on "obviousness – common general knowledge".

[58] There is some authority in this Court that favours blinded witnesses. However, I am of the view that blinding can be overrated. It may be a factor in giving weight but the Court is more interested in the substance of the opinion and the reasoning behind the conclusions. In that respect my conclusion is similar to that in *Shire Canada Inc v Apotex Inc*, 2016 FC 382, 265 ACWS (3d) 456.

[59] Blinding may in some cases be unhelpful because the opinion lacks proper context. In other cases blinding will produce a less cluttered opinion. In the present case I do not favour Apotex's experts simply because they were blinded. I would favour their opinions on the POS and common general knowledge because they offered stronger reasons for their position. Some of Apotex's witnesses, Nam for example, provided confusing and at times contradictory statements on utility and non-infringement.

B. *Burden of Proof*

[60] The parties are not seriously in dispute as to the legal test; they are at odds as to whether the test has been met.

[61] As Janssen argues, that in accordance with the Act, the 422 Patent is presumed to be valid in the absence of evidence to the contrary. Apotex has the burden of giving its allegations an air

of reality by leading evidence that is not clearly incapable of establishing the allegations (see *Leo Pharma Inc v Teva Canada Limited*, 2015 FC 1237, 262 ACWS (3d) 1024, aff'd 2017 FCA 50).

Once that burden is met, Janssen must show on the balance of probabilities that the allegations are not justified.

[62] It is fair to say that in large measure Apotex has met the burden of "an air of reality" on the issue of validity. On the matter of infringement, Apotex is not as strong. However, this case does not turn on the narrow knife edge of burden of proof.

[63] On the issue of eligibility for patent listing, the burden is different. This is so because the allegation is not one listed in s 5(1) of the Regulations. As a result, Apotex has the burden of showing that the 422 Patent is not eligible for listing on the patent register.

C. *Claim Construction*

(1) The Person of Ordinary Skill

[64] The definition of the POS is simple – its determination less so. As held in *Free World Trust v Électro Santé Inc*, 2000 SCC 66 at para 44, [2000] 2 SCR 1024 [*Free World*], such a person is "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". The question is who works the patent in the real sense.

[65] According to Janssen's experts, Auchus, Rettig and So, the POS for the 422 Patent is a physician specializing in urology or medical oncology with significant practical experience in the treatment of patients with prostate cancer. They would work in a team or have access to individuals with expertise in endocrinology, biochemistry, pharmacology, and/or molecular biology or a related field of science with experience in prostate cancer treatments or androgen synthesis and action.

[66] Apotex agrees that the POS is a notional person with skills in the art to which a patent relates and agrees that the 422 Patent is generally directed to medical doctors such as urologists and medical oncologists who are involved in treating patients with prostate cancer. However, it disagrees that the POS would have had access to individuals with expertise in endocrinology.

[67] There is no evidence that a urologist or oncologist would consult an endocrinologist to select a treatment for prostate cancer. Nam testified that he has never consulted an endocrinologist in practice. Dr. So also said that he considers himself and other urologists and medical oncologists who treat prostate cancer to be endocrinologists – therefore, they would not need to consult a board-certified endocrinologist.

[68] The fact that potentially an urologist or oncologist might consult an endocrinologist from time to time is not evidence that the POS includes such a skill in order to understand and use the Patent. There is no evidence that a POS needs to know in micro-detail how the drug works when treating a patient.

[69] I find that the POS would be a hypothetical physician specializing in urology or medical oncology with significant practical experience in the treatment of patients with prostate cancer. I agree with Apotex that little evidence supported that a urologist or medical oncologist would consult with an endocrinologist when making treatment decisions. Dr. So's admission in cross-examination indicated that urologists and medical oncologists have enough endocrinology knowledge to interpret and apply the 422 Patent. As the 422 Patent focusses on the use of medications to treat cancer, it makes sense that the POS would be a physician who would be determining courses of prostate cancer treatment.

[70] The POS would have read any new scientific literature in the field, attended scientific conferences and meetings, and discussed new developments and ideas with colleagues.

[71] However, this does not mean that the Court cannot consider the evidence of Auchus and Prins. Expert evidence as to the state of the art does not need to come from a person who would be a POS as long as the evidence provided by the witnesses describes information that the POS would have known and understood at the relevant time: *Halford v Seed Hawk Inc*, 2006 FCA 275 at para 17, 54 CPR (4th) 130. Both Auchus and Prins provide some information about hormone synthesis that is helpful for the Court to understand and does not appear to go beyond the knowledge of the POS. I therefore dismiss Apotex's contention that Auchus' evidence should be rejected.

(2) <u>The Common General Knowledge as of the Filing Date and Publication Date</u>

[72] The scientific background described at the beginning of these Reasons appears to be accepted common general knowledge as of 2007 according to the expert evidence. The parties also agree that there is little difference between the common general knowledge and the state of the art. This section describes the contested parts of the common general knowledge.

[73] Janssen argues that the 59 documents put forward by Apotex that focus on CYP17 inhibitors and their ability to block androgen production are not representative of the state of the art, as they represent a small subset of the nearly 20,000 results of a search for "treatment" and "prostate cancer" in PubMed. Apotex's experts could not fully explain how the 59 documents were gathered or why a POS would have searched for "abiraterone acetate" specifically in their keyword search. There was nothing to set AA apart from other compounds being investigated in 2007. A number of better compounds for inhibiting CYP17 were disclosed in the 213 Patent.

[74] Janssen argues that as of 2007, how or why patients developed CRPC was unknown, but that the prevailing view was that CRPC had become independent of androgens, so controlling residual androgens was not a priority. Researchers had moved away from secondary hormonal agents to treat mCRPC because there was no evidence of improved clinical outcomes, with one researcher even saying that further hormonal manipulations were "futile". This is supported by the testimony of Rettig and Auchus. There were a number of theories for how CRPC developed including mutations to the androgen receptors, the over-expression of androgen receptors, the activation of the receptors by non-androgen compounds, or the prostate cancer cells becoming independent of the androgen receptor. There were over 200 experimental compounds being developed as of 2007.

[75] Although kenoconazole [KC] and aminoglutethimide [AG] had been investigated as potential prostate cancer treatments, they had not been shown to have a survival benefit or any meaningful outcome, nor had they been approved for prostate cancer treatment. Both agents inhibit the production of all adrenal steroid hormones and the enzyme responsible for the production of all glucocorticoids. Therefore KC was sometimes used off-label to manage overproduction of glucocorticoids and mineralocorticoids. Although KC inhibits the CYP17 enzyme, AG does not.

[76] It was known in 2007 that KC and AG caused side effects related to suppressed glucocorticoid production. Therefore glucocorticoids were sometimes administered with KC and AG treatments. O'Donnell 2004, however, reported that KC and AG could be administered effectively and safely without glucocorticoids.

[77] As of 2007, PN was sometimes used for its palliative effects in relieving pain and inflammation from cancer or for relief from the side effects of cytotoxic chemotherapy. It was not approved for any cancer treatment and was not known to provide a survival benefit in prostate cancer patients. Glucocorticoids were only administered as a last resort to cancer patients for palliative relief or when medically indicated for a clinical disorder. Glucocorticoids were associated with serious impacts, including limiting the ability for the adrenal glands to produce glucocorticoids.

[78] Mineralocorticoid excess was not usually treated with glucocorticoids; it was treated with mineralocorticoid receptor antagonists like eplerenone, anti-hypertensives, diuretics, and/or potassium supplements.

[79] Janssen says that nothing set AA apart from the other compounds being researched for the treatment of prostate cancer. In addition, there were a number of CYP17 inhibitors disclosed in the 213 Patent that were more potent inhibitors of CYP17 than AA.

[80] AA had been investigated in Phase I clinical trials for the treatment of prostate cancer, but had not been tested for its efficacy in the treatment of prostate cancer. It had a different mechanism of action than KC and AG as it only specifically inhibited the CYP17 enzyme. It preferentially inhibited the 17,20-lyase activity of CYP17, which allowed for the production of cortisol to continue. Corticosterone could also continue to be produced. AA was not expected to cause the same side effects as KC and AG and it was not expected to cause mineralocorticoid excess, adrenal insufficiency or low adrenal reserve. Importantly, at that time in 2007, there was no reason to think glucocorticoid replacement was needed with AA treatment.

(a) *Apotex*

[81] Apotex states that the state of the art and common general knowledge in 2007 indicated that treatment of CRPC required second-line hormone therapy to reduce residual androgens produced by the adrenal gland. The drugs used to inhibit residual adrenal androgens caused significant side effects and required glucocorticoid replacement therapy. O'Donnell 2004 stated that the testosterone suppression from AA treatment warranted further clinical study as a second-

line hormonal treatment for prostate cancer. The 422 Patent itself also does not suggest that it is unique in discovering a link between androgens and mCRPC.

[82] There was a large body of literature indicating that reducing residual androgen levels would provide a clinical benefit. Rettig in challenging this notion has cited only an obscure article, Lara and Meyers 1999 to support his statement. In contrast, Lam 2006, whose authors included an inventor of the 422 Patent, stated that secondary hormonal therapy to lower androgen levels was thought to be a cornerstone of management for advanced prostate cancer and expressed the hope that further studies would show clinical response.

[83] Apotex argues that the use of KC and AG for prostate cancer treatment led to the development of AA. The use of AG showed short survival benefits and pain improvement when administered with glucocorticoids. Kruit 2004 indicated that PSA levels decreased when patients were treated with AG. The side effects from AG limited its effectiveness. KC was widely used for treating CRPC in the early 2000s as it inhibited the CYP17 enzyme and therefore suppressed the production of testosterone. In Lam 2006, KC was described as the "most active second line hormonal therapy." Phase III clinical trials showed that KC had clinical benefit and PSA responses. Similarly, KC had side effects of adrenal insufficiency, which could be partially but not completely managed with a glucocorticoid.

[84] Apotex relies on Rettig's admission on cross-examination that he had prescribed KC with PN to treat prostate cancer patients prior to 2007. In 2007, clinical practice guidelines used by oncologists suggested the use of KC for mCRPC patients. KC and AG were widely used off-

label to treat prostate cancer patients. The context of that admission – a last desperate treatment – undermines the force of the statement Apotex would like it to be.

[85] The inventors of the 213 Patent described the activity and side effects of KC treatment as showing the need to design a drug like AA that inhibits the CYP17 enzyme more specifically. O'Donnell 2004 also noted that the side effects of KC and AG supported the development of AA as a more selective inhibitor.

[86] On the matter of PN and glucocorticoids in treating prostate cancer, by August 2007, PN was known for its use as an anti-cancer agent, glucocorticoid replacement therapy, and for the palliative treatment of end-stage prostate cancer. PN and other glucocorticoids were described as having anti-cancer activity, causing PSA decreases of more than 50% in some patients, and lowering adrenal androgen levels. PN was included in several Phase III trials in combination with other drugs because it was useful for pain relief and exhibited anti-cancer activity.

[87] PN was also used in combination with KC and AG to replace glucocorticoids that were suppressed as a side effect of KC and AG. PN was also the standard of care for palliative treatment for end-stage prostate cancer patients. Therefore Apotex argues PN was used as the control for any study when evaluating new drugs.

[88] Further, Apotex argues that PN was a common glucocorticoid treatment and would be the logical choice for prostate cancer patients because of its palliative and anti-cancer effects.

Studies of PN showed PSA declines of more than 50%, although there was no shown survival benefit.

[89] In terms of the use of AA in prostate cancer treatment, Apotex says that AA was developed as a progression of the work with KC and AG. It inhibited CYP17 more selectively than AG or KC. According to Attard 2005, inhibition of the CYP17 enzyme was the "logical target" for treating CRPC. Some side effects were still expected from AA, although it was more selective than AG or KC. O'Donnell 2004 showed that when administered to men with recurring prostate cancer, AA could cause sustained suppression of testosterone. The authors of O'Donnell 2004 noted that AA was potentially useful in the secondary hormone treatment of prostate cancer and that the side effects of AA may require glucocorticoid replacement. Subsequent commentary about the O'Donnell 2004 study prior to 2007 described AA treatment as being under development with clinical trial results keenly awaited where patients would be monitored for glucocorticoid insufficiency.

[90] AA was different from other options for CRPC treatment. Attard 2005 described AA as having a mechanism of action particularly attractive for use in CRPC treatment. Although other compounds might have shown more potent inhibition of the CYP17 enzyme, only AA had been tested in humans, as reported in O'Donnell 2004.

[91] Apotex argues that the 422 Patent did not claim the invention of AA to treat prostate cancer. Instead at para 35 of the 422 Patent disclosure, it cited the 213 Patent as indicating that

CYP17 inhibitors were useful in the treatment of hormone dependent cancers like prostate cancer. No prior art or witness has indicated that AA was viewed by any in the field as a failure.

[92] AA was not known to preferentially inhibit the 17,20-lyase activity of CYP17. O'Donnell 2004 indicated that AA could affect patients' cortisol levels and could be expected to possibly cause adrenal insufficiency or mineralocorticoid excess, which might require glucocorticoid replacement therapy. De Bono's trials showed that there was an expectation of side effects that may have required glucocorticoid replacement.

(b) *Court's Conclusions re Disputed General Knowledge*

[93] As noted earlier, the parties' positions on common general knowledge and prior art do not clearly distinguish between what is prior art and what is common general knowledge. They say in argument that they are basically the same.

[94] However, legally they are not the same. "Prior art" is any publically available teachings, even if it is obscure or not generally accepted: *Mylan Pharmaceuticals ULC v Eli Lilly Canada Inc*, 2016 FCA 119 at para 23, [2017] 2 FCR 280 [*Mylan*]. Common general knowledge is the "knowledge generally known by persons skilled in the relevant art at the relevant time": *Apotex Inc v Sanofi-Synthelabo Canada Inc*, 2008 SCC 61 at para 37, [2008] 3 SCR 265 [*Sanofi*].

[95] The Federal Court of Appeal in *Mylan* at para 25 described the use of prior art and common general knowledge as follows:

> Prior art is used for specific purposes in patent law, such as to found an allegation that prior art anticipated the invention or rendered it obvious. The common general knowledge informs the way in which the claims and specifications are read, because it is to the skilled person that the patent is addressed. Any inquiry in patent law that is performed from the perspective of a skilled person will import the common general knowledge.

[96] Outlined below is the Court's conclusion on the common general knowledge. The relevant prior art is discussed in the obviousness analysis to follow later in these Reasons.

[97] The relevant date for common general knowledge for claim construction is the Publication Date, February 28, 2008: see *Free World* at para 54. The relevant date for obviousness and utility is the common general knowledge as of the Filing Date, August 23, 2007. The parties did not indicate that the common general knowledge was different between the Filing Date and the Publication Date. Janssen's expert, Dr. So, provided his view on common general knowledge and claims construction from the publication date. His evidence did not indicate that the common general knowledge changed between August 2007 and February 2008. Therefore, the Court accepts that the common general knowledge of the POS was essentially the same between the two dates.

[98] The Court does not accept Janssen's proposed method of determining the common general knowledge by referring to the nearly 20,000 articles on prostate cancer treatment that were available on PubMed in 2007 and suggesting that a POS would not have been able to focus on adrenal androgen inhibitors. The idea that a POS would merely have searched the words "prostate cancer" and "treatment" as a way to keep up to date with the latest research on end-stage prostate cancer treatment is not realistic.

On the other hand, Nam's evidence that a POS would have focussed on AA specifically as a potential treatment option is also difficult to accept, although the O'Donnell 2004 report was clearly part of the prior art. It is not established that O'Donnell 2004 was considered to be part of common general knowledge. There was not enough evidence to show any general acceptance of AA as a treatment for prostate cancer as of 2007.

[99] However, the Court would find that as of 2007, the POS would know that suppressing residual adrenal androgens could be useful in the treatment of mCRPC and was an active area of research. I accept that the mechanisms for the development of mCRPC were not fully known, however residual adrenal androgens were thought to likely play a role.

[100] Although no clinical trial had shown a survival benefit and the drugs used had shown significant side effects, the fact that researchers continued to explore the area of residual androgens and secondary hormonal therapy for prostate cancer between the 1990s and 2000s indicates that researchers had not moved away from the theory.

[101] Lam 2006, a review article cited both by Rettig and Nam, concluded that secondary hormonal therapy was an "active area of research" and stated in its abstract that secondary hormonal therapy was "an excellent therapeutic option in patients with AIPC whose primary hormonal therapy [had] failed." This article also noted that KC, as an adrenal androgen inhibitor, was the most active second line hormonal therapy despite its significant side effects.

[102] Further, the Court finds that the POS would know that, as of 2007, adrenal androgen inhibitors such as KC and AG could have some short-term anti-cancer effects for late-stage prostate cancer patients, although with serious side effects. The POS would have especially considered KC as a potential last-resort treatment option because its mechanism appeared to be better understood than the mechanism of action for AG.

[103] This finding aligns primarily with the evidence put forward by Nam who cited a number of studies as well as the US National Cancer Care Network recommendations at the time to show that KC was a recommended treatment for advanced prostate cancer as of 2007, despite the lack of demonstrated survival benefit.

[104] KC was known to inhibit desmolase, CYP17 enzyme, and 11β-hydroxylase. AG was known to inhibit desmolase, 11β-hydroxylase, and aromatase. Both drugs therefore were known to be relatively unselective and inhibit a number of adrenal steroids.

[105] The Court also finds that the POS would know to prescribe a glucocorticoid if administering KC or AG, because of the known adrenal insufficiency caused by the drugs. Although Rettig initially suggested that KC and AG were not known to be clinically effective for the treatment of prostate cancer, he also admitted that at the time he would prescribe KC with a glucocorticoid as a "last resort" for his patients with CRPC. While not as damning an admission as Apotex contends, it shows the general direction of the Common General Knowledge.

[106] Although one must be careful to not equate a specific person with the POS, Rettig's practice supports Nam's opinion that the POS would have at least known about KC as an option for treatment with the potential for significant side effects that could be partially treated with co-administration with a glucocorticoid.

[107] In addition to the number of studies from the 1980s to 2000s cited by Nam, O'Donnell 2004 further supported that it was "common practice to administer supplementary hydrocortisone" when treating prostate cancer with KC or AG. Although O'Donnell 2004 indicated that some older studies showed that glucocorticoids might not be necessary, the common general knowledge by 2007 appeared to be that glucocorticoids should be co-administered with KC and AG.

[108] However, I cannot find that KC or AG were known to cause mineralocorticoid excess as common general knowledge. Auchus explained that the inhibition of desmolase by KC and AG were known to suppress all adrenal androgens, therefore neither would be expected to cause mineralocorticoid excess – as mineralocorticoids would also be expected to be suppressed. In addition, Prins appeared to be generalizing broadly when she suggested that both KC and AG could cause mineralocorticoid excess. She noted in her cross-examination that at low doses, KC primarily inhibits the CYP17 enzyme, however it is unclear what she meant by low doses and whether this compares to the doses given for treating prostate cancer. She admitted that AG did not inhibit the CYP17 enzyme and that KC also inhibited corticosterone.

[109] This appears to then agree with Auchus's conclusion that KC and AG could be expected to cause adrenal insufficiency, but not necessarily mineralocorticoid excess. There was some prior art, such as De Coster 1987, which indicated that KC could possibly cause mineralocorticoid excess. However, other more recent articles, such as Lam 2006 and Small 2004, appeared to more generally indicate that KC was known to suppress all adrenal steroids and therefore cause adrenal insufficiency.

[110] With respect to PN in the treatment of prostate cancer, I would find that a POS would know that PN was used for its palliative effects and in glucocorticoid replacement therapy. PN was the standard of palliative care for end-stage prostate cancer, which meant that it was usually given to patients in the control arm of studies. The POS would know that PN was a potential anti-cancer agent, but with only moderate and short-term effects.

[111] Although PN was known for its palliative effects in prostate cancer patients and its reduction of adverse side effects from chemotherapy, the Court concludes that PN on its own for effective prostate cancer treatment was not part of the common general knowledge at the relevant dates.

[112] Unlike KC, AG, and AA, there was little evidence presented that indicated that PN was being actively researched as a cancer therapy on its own in 2007. According to Lam 2006, a review article on secondary hormonal therapy, glucocorticoids had not been significantly studied separately for their anti-cancer effects because they were usually used as a control arm for other trials. The article did suggest that they should be considered "active hormonal agents for prostate

cancer." Many of the studies cited by Nam mostly studied PN in combination with other drugs, and sometimes attributed some anti-cancer effects to the glucocorticoids.

[113] In addition, I do not find that a POS in 2007 would have been overly concerned about side effects or carcinogenic effects from prescribing glucocorticoids like PN to patients with mCRPC. Rettig and Auchus did not cite any recent articles that indicated any concerns about PN for use with prostate cancer, especially since Rettig admitted that PN was used for palliative effects in prostate cancer patients and to reduce side effects from chemotherapy. As put forward by Nam, it seems logical that a POS would be less concerned with the potential long-term effects of PN when treating a patient with end-stage prostate cancer than when treating a patient with another disorder.

[114] In respect of AA's use in prostate cancer treatment, Apotex has not shown that O'Donnell 2004 was part of the POS's common general knowledge as of 2007. Although O'Donnell 2004 was cited in a few review articles between 2004 and 2006, AA had not been generally accepted by people engaged in the art as an anti-cancer drug. There is no evidence that AA was being used by urologists or medical oncologists as a treatment for prostate cancer other than in the O'Donnell study and the Cougar trials.

[115] It was common general knowledge that a more selective adrenal androgen inhibitor than KC and AG could more effectively treat prostate cancer with fewer expected side effects.

(3) Claim Construction Analysis

[116] As noted in paragraph 38, the claims at issue are 3, 6, 7, 14 and 15. Each of the claims refer to the use of a therapeutically effective amount of AA (or an acceptable salt thereof) and a therapeutically effective amount of PN for the treatment of a prostate cancer in a human. [Underlining by Court]

[117] The dispute between the parties is whether each of AA and PN amounts must be therapeutically effective in the treatment, as argued by Apotex, or whether the combination of the two drugs to treat prostate cancer is the proper construction.

[118] A patent must be read purposefully with the knowledge of a POS with a mind willing to understand who is trying to achieve success and is not looking for difficulties or seeking failure. Claim construction is a question of law (*Whirlpool Corp v Camco Inc*, 2000 SCC 67 at paras 43, 49-50, 61, [2000] 2 SCR 1067).

[119] It is essential to refer to the definition of terms in the Patent:

a) "therapeutically effective amount of AA" and "therapeutically effective amount of PN": an amount of AA effective for treating prostate cancer and an amount of PN effective for treating prostate cancer.

b) "treatment" (and "treating") includes the eradication, removal, modification, management or control of a tumour or primary, regional or metastatic cancer cells or tissues and the minimization or delay of the spread of cancer.

c) "refractory prostate cancer": prostate cancer that is not responding to an anti-cancer treatment or prostate cancer that is not responding sufficiently to an anti-cancer treatment, which can also include recurring or relapsing prostate cancer.

[120] Interpreting the claims is the judge's function although they can be assisted by the expert evidence. In this case the relevant experts are at odds.

[121] On a plain reading of the claim, the amounts of AA and PN are circumscribed by the adjectival phrase "therapeutically effective amount". Nam read the claim as reading in the word "each". While Janssen thinks that this is a damaging error in interpretation. I find it to be a reasonable one.

[122] The inventors chose to fence in the amount of each substance with the descriptor. Janssen's interpretation would have the effect of reading out "therapeutically effective amount". Janssen would have it that any amount of either, so long as used in combination to treat cancer, is sufficient to fall within the claim.

[123] Given that at the time PN was known by POS to have palliative effectives, the insertion of words that indicate that the role of PN (and AA) are to attack the cancer and in a meaningful way, gives meaning and significance to the descriptor.

[124] It is evident that the claim is to the cancer fighting feature of PN not its palliative effects.

[125] In my view, Apotex's interpretation is the correct one. Even if there was some confusion or ambiguity, recourse to the Disclosure confirms as reference that the amount of inhibitors or of steroid is an amount sufficient to treat cancer, whether administered alone or in combination. However, there is no need to refer to the Disclosure.

[126] The Asserted Claims claim the use of therapeutically effective amounts of AA and of PN in combination to treat prostate cancer.

[127] This raises the question of whether the 422 Patent claims a combination of AA and PN that has an effect beyond the known effects of its component parts. Although this is a question of claims construction, it is discussed below as a separate matter.

D. *Patentable Subject Matter*

[128] It was Janssen's position that the Asserted Claims are patentable subject matter because the combination of AA and PN resulted in an anti-cancer effect that was not observed when either drug was administered alone. The combination is patentable because the elements cooperated in an unexpected manner or cooperated in a known way to give an unexpected result.

[129] There is legal support for this proposition in *Gilead Sciences Canada Inc v Canada (Minister of Health)*, 2012 FC 2, 403 FTR 86. Janssen's authority, *Bridgeview Manufacturing Inc v 931409 Alberta Ltd (Central Alberta Hay Centre)*, 2010 FCA 188, 191 ACWS (3d) 235 [*Bridgeview*], is more focussed on obviousness than patentable subject matter.

[130] Apotex argues that the Asserted Claims claim non-patentable subject matter as the subject matter of the Asserted Claims is the combination of two known anti-cancer agents.. The 422 Patent claims the use of two anti-cancer agents together without suggesting any synergistic result. As phrased by Apotex, to be patentable subject matter one drug plus one drug must be more effective than just two drugs together.

[131] I have concluded that the 422 Patent claims patentable subject matter and therefore Apotex's allegation of non-patentable subject matter is not justified.

[132] The parties appear to have mixed together their arguments on patentable subject matter and whether the utility of the combination was demonstrated. To be a patentable combination, the 422 Patent must claim a combination with effects different from the sum of the effects of the elements: *R v American Optical Co*, [1950] Ex CR 344, 13 CPR 87 at 98-99; *Eli Lilly Canada Inc v Apotex Inc*, 2018 FC 736 at paras 71-72, 156 CPR (4th) 387 [*Eli Lilly*]. The issue regarding patentability of the subject matter is whether the 422 Patent reads from the perspective of the POS as claiming a combination with synergistic effect or effects beyond those of either component drug. The issue of whether any effectiveness of the combination was demonstrated or soundly predicted is separately addressed in the discussion of utility.

[133] For the claimed combination to be patentable, the Asserted Claims supported by the disclosure of the 422 Patent from the perspective of a POS must claim that the combination of AA and PN has a greater effect than either component alone.

[134] Unlike in *Eli Lilly*, the 422 Patent does not disclose any test data suggesting that there is a synergistic or interacting effect between a CYP17 inhibitor like AA and the other therapeutic agent, such as PN. However, in *Eli Lilly* one of the components in the combination was already used as a monotherapy and the other component was part of a class that was commonly used as a monotherapy for treating the same condition.

[135] In contrast, neither AA nor PN were known in the common general knowledge as an effective monotherapy for the treatment of prostate cancer, although pre-cursor adrenal androgen inhibitors were known to be used to treat prostate cancer in combination with glucocorticoids to treat side effects. The 422 Patent at para 35 describes CYP17 inhibitors like AA as being useful for the treatment of prostate cancer as described in the 213 Patent. In addition, common general knowledge was that PN had a modest short-term anti-cancer effect, but was not a commonly used monotherapy for its anti-cancer effects.

[136] The experts differed as to whether the 422 Patent disclosed a synergistic or enhanced effect when AA was combined with PN. Rettig concluded that because a POS would understand that neither AA nor PN was effective or used as a monotherapy to treat prostate cancer, the combination of AA and PN indicated an anti-cancer effect when they were combined. Rettig did not specifically find that the language of the 422 Patent disclosed a synergistic effect of the two compounds, in his view the common general knowledge was that neither AA nor PN was effective at treating prostate cancer as a monotherapy. Nam disagreed, finding that the 422 Patent did not disclose or claim any synergistic effect between AA and PN. He found that as both drugs were known to be useful as anti-cancer agents, their combination would be expected to just have additive anti-cancer effects.

[137] The 422 Patent claims an enhanced effect when AA and PN are combined for the treatment of prostate cancer. Although the amounts of CYP17 inhibitor and glucocorticoid described in paras 43 and 54, respectively, indicate that each agent has some anti-cancer effect on its own, the Asserted Claims only describe the combined use of AA and PN. Claim 15 in

particular describes the use of the combination to treat prostate cancer that is not responding to at least one anti-cancer agent. Based on the definition of anti-cancer agent in the 422 Patent, this could include the use of any agent on its own that has an anti-cancer effect, including AA or possibly PN.

[138] Paragraphs 6 and 7 of the 422 Patent state that patients administered hormone therapy show variable responses and may have cancer recur. The 422 Patent indicates at paragraph 8 that the combination of a CYP17 inhibitor with another anti-cancer therapeutic agent could treat refractory cancer, which includes a cancer that is not sufficiently responding to an anti-cancer treatment.

[139] To the extent that an anti-cancer treatment could include either treatment with AA alone or PN alone, then the 422 Patent would be read by the POS to claim that the combination of PN and AA treats prostate cancer in a way that overcomes resistance to other anti-cancer therapies, including AA or PN used on their own.

[140] I note Nam's conclusion that merely combining two drugs thought to possibly have anti-cancer effects would obviously result in their additive anti-cancer effect. As indicated in the expert evidence, PN and AA both affect the adrenal androgen synthesis pathway, and their full effects and interactions in this pathway were not commonly known in 2007.

[141] It is sufficient in this case that the 422 Patent claims an improved anti-cancer effect than each of AA or PN treatments on their own. Given that neither AA and PN had actually been

shown to have a long-term anti-cancer effect, it may be impossible to ask that a patent predict and differentiate between an additive effect of AA and PN together and a synergistic effect.

[142] The Court in *Eli Lilly* at para 91 did not require that the claim be one of synergy, as long as the claim disclosed a combination that was more effective than the sum of the effects of the agents used alone. In this case, the effects of the agents used alone were not well-established prior to the Filing Date. The combination is claimed to be more effective and absent other evidence, Apotex's allegation of non-patentable subject matter has not been justified.

E. *Obviousness*

[143] Janssen argues that Apotex's allegation that the Asserted Claims would have been obvious to the POS as of the Claim Date (August 23, 2007) is not justified. The invention is not obvious under section 28.3 of the Act.

[144] There is no dispute as to the legal test as laid out in *Sanofi* at para 37. The question in assessing obviousness is whether a POS would, in light of the state of the art and common general knowledge, and without knowledge of the invention as claimed, have come directly and without difficulty to the solution taught by the patent. The test for obviousness is set out in *Sanofi* at paras 67-69:

1. Who is the notional POS?

   What is the relevant common general knowledge of the POS?

2. What is the inventive concept of the claim, or the claim as construed?

3. What are the differences between the state of the art and the inventive concept or the claim as construed?

4. Without any knowledge of the alleged claimed inventions, would the differences between the state of the art and inventive concept have been obvious to the POS or do they require any degree of invention?

For combination inventions, a failure to identify the inventive concept may result in an erroneous focus on individual elements: *Bridgeview* at paras 51-52.

[145] To assess whether the claimed invention was obvious to try, the Court may apply a number of factors to assess whether it was "very plain" or "self-evident" that the invention would work: *Pfizer Canada Inc v Apotex Inc*, 2009 FCA 8 at para 29, [2009] 4 FCR 223.

(1) POS/Common General Knowledge

[146] The parties' positions on the POS and common general knowledge have already been outlined.

(2) Inventive Concept

[147] With respect to the inventive concept, the parties essentially agree that the inventive concept of the Asserted Claims is the use of AA and PN, in therapeutically effective amounts, for the treatment of prostate cancer, including refractory prostate cancer. However, as in Claim Construction, Apotex maintained that "therapeutically effective amount" is the amount of AA or PN, each effective for treating prostate cancer, rather than an amount effective when the two drugs are combined.

(3) Difference: State of Art/Inventive Concept

[148] The parties have very different views on the differences between the state of the art [SOA] and the inventive concept. As earlier described, Janssen rejects Apotex's assertion that the 59 documents that focussed on compounds inhibiting the CYP17 enzyme and blocking androgen production were representative of SOA.

[149] In this regard, Janssen argues the following differences between the SOA in 2007 and the inventive concept:

- The role of residual adrenal androgens in CRPC was not known and there was no known benefit of reducing androgens below castrate levels;
- KC and AG were not known to have an anti-cancer effect and were known to have serious side effects. They were given to patients as a last resort.
- AA was not a known anti-cancer treatment in 2007. Previous studies on AA showed a short-term reduction in testosterone levels, but not clinical efficacy in the treatment of prostate cancer.
- Unlike KC and AG, AA would not be expected to require glucocorticoid replacement because AA allowed some cortisol to be produced and did not at all inhibit the production of corticosterone.
- PN was not known to treat prostate cancer by contributing to any anti-cancer effect.
- AA was not known to cause mineralocorticoid excess or adrenal insufficiency. Partial inhibition of cortisol production at times of stress did not cause adrenal insufficiency or mineralocorticoid excess.
- Different drugs or management options would be preferable over PN to manage mineralocorticoid excess or adrenal insufficiency.
- Prior art did not teach administration of a glucocorticoid like PN with AA.

[150] Apotex argues that obviousness is not determined by referring to the prior art at large. Apotex as the second person must point to one or more elements of prior art that make the invention in the 422 Patent obvious. The choice of these prior art elements are limited only by the fact they must be public prior to the claim date according to section 28.3(b) of the Act. If there is a gap between the claimed subject matter and the prior art, then the assessment is whether the POS could bridge the gap using the common general knowledge and prior art that could be discovered by a reasonably diligent search: *Ciba Specialty Chemicals Water Treatments Limited v SNF Inc*, 2017 FCA 225 at para 62, 152 CPR (4th) 239 [*Ciba*].

[151] Apotex asserts that the only difference between the SOA and the subject matter/inventive concept of the 422 Patent is that AA and PN had not actually been combined and administered in the treatment of prostate cancer. Both AA and PN were already known as anti-cancer agents for the treatment of prostate cancer, as well as refractory prostate cancer.

[152] The following points were already known in the prior art:

- AA reduced testosterone levels in prostate cancer patients and could be useful in secondary hormone therapy for patients with refractory prostate cancer, with additional clinical trials planned (O'Donnell 2004).
- KC and AG were known to be beneficial in the treatment of prostate cancer and AA as a more selective inhibitor was expected to be just as effective or more effective than KC and AG (Potter 1995, O'Donnell 2004, 213 Patent).
- PN and other glucocorticoids had demonstrated anti-cancer activity, including observed PSA responses in patients with CRPC, both alone and in combination with other drugs, including KC (Sartor 1998, Fossa 2001, Berry 2002, Harris 2002, Small 2004, Lam 2006, Yano 2006).

(4) Obviousness/Degree of Invention

[153] Janssen, in summary on this issue, makes the following points:

- There is no suggestion in the art that combining AA and PN would be useful in treating prostate cancer especially where the cancer had progressed after being treated with each drug alone.
- The prior art suggested that there were hundreds of potential therapies with different mechanisms of action being explored to treat prostate cancer as of 2007. There was no motivation to develop a secondary hormonal therapy for the treatment of prostate cancer. None of the decades of research had shown that secondary hormonal therapy could improve survival. There was little data to support that residual androgens were important in stimulating prostate cancer growth in mCRPC patients. Therefore, a skilled person would not have given PN or any glucocorticoids to a patient unless there was a clear clinical need.
- The inventors' course of conduct was arduous and counter-intuitive. The clinical trials were expensive, time-consuming, and uncertain. It would have been difficult to get approval to study the combination of two drugs that were unsuccessful when given individually.
- It would not be self-evident to combine two failed treatments with the expectation that they would have an effect in combination. De Bono's study was the first study that suggested that a glucocorticoid with AA could reverse resistance and result in a prolonged response.

[154] Apotex, on the other hand, argues that the subject matter of the Asserted Claims in the 422 Patent would be obvious at the claim date to a POS under section 28.3 of the Act.

[155] In its analysis of the *Sanofi* test, Apotex makes the following points:

- In determining the prior art, the person alleging obviousness can select the pieces of prior art that make the impugned invention obvious, limited only by section 28.3 of the Act: *Ciba* at para 60.
- In the second step of the *Sanofi* test, the Federal Court of Appeal in *Ciba* has indicated that the Court should usually focus on construing the claim rather than attempting to determine the broader inventive concept of the claims.
- The fourth *Sanofi* step is assessed by looking at whether the differences between the inventive concept (or the claim as construed) and the prior art can be bridged by a POS using only their common general knowledge and other information which they could have found by making a reasonably diligent search.
- In determining whether the invention was obvious to try, the Court should consider whether a POS would find it more or less self-evident to try to obtain the invention, including assessing the extent, nature and amount of effort required to achieve the invention and the motivation to find the solution provided by the patent. To be obvious to try, a POS just needs to have a fair expectation of success, but does not need to be able to predict success with certainty: *AstraZeneca Canada Inc v Teva Canada Ltd*, 2013 FC 245 at para 43, 428 FTR 269.

[156] Apotex goes on to argue that bridging this difference between the SOA and the inventive concept was obvious and obvious to try as there was no inventive ingenuity required to use two drugs known for anti-cancer effects together as anti-cancer agents in the treatment of prostate cancer. There was no reason that the known anti-cancer effects of PN and AA would be diminished when combined. The POS would understand that AA and PN had different mechanisms for suppressing testosterone.

[157] Apotex rejects the evidence of Rettig that a PubMed search produced 20,000 articles on prostate cancer and treatment is representative of what a POS would search for. The Court agrees with Apotex that a POS would have performed a more narrow search and been led to AA because of the Attard 2005 article. Apotex generally challenges Rettig's evidence on prior art and common general knowledge because he relied on documents supplied by counsel.

[158] Apotex argues that de Bono's clinical trials to test AA and PN were routine and would have been the same types of trials conducted to test AG and KC. The POS was extremely motivated to arrive at the solution in the 422 Patent and would have combined AA and PN to mitigate the predictable side effects of AA. The solution of combining AA and PN to treat prostate cancer was one of a limited number of solutions following the experience with KC and AG.

[159] Finally, in the same vein, Apotex argues establishing that AA and PN would be useful for the treatment of prostate cancer would have involved the same routine work already done with

KC and AG in combination with a glucocorticoid. The clinical trials conducted by de Bono were routine and not inventive.

(5) Court's Conclusions on Obviousness

(a) *Step 1: POS and Common General Knowledge*

[160] As stated above, the POS is a physician such as a urologist or medical oncologist with significant experience treating prostate cancer. They would remain current with developments in the treatment of cancer and would have been aware that secondary hormonal therapy was an active area of research. They would know that KC, which was used as a last resort therapy, had to be used with glucocorticoids to prevent adrenal insufficiency. They would be aware that a more specific CYP17 inhibitor would likely be effective in reducing adrenal androgens with fewer side effects.

(b) *Step 2: Inventive Concept or Claim Construction*

[161] Although Apotex has argued that the Federal Court of Appeal in *Ciba* at para 77 has recommended that the Court avoid using the "inventive concept" in the second step of the *Sanofi* test, the Federal Court of Appeal cannot overturn or change the *Sanofi* test set out by the Supreme Court of Canada.

[162] As stated by Justice Fothergill in *Apotex Inc v Shire LLC*, 2018 FC 637 at paras 115-117, 294 ACWS (3d) 606 [*LDX*], the Court should still attempt to determine the inventive concept of a patent, especially one concerning pharmaceutical compounds like in *Sanofi*. In this case, as

with the *LDX* case, the Court can identify the inventive concept of the Asserted Claims without distraction or engaging in unnecessary satellite debate.

[163] The inventive concept has already been discussed.

(c) *Step 3: Differences between the State of the Art and Inventive Concept*

[164] The Court concludes that Apotex has stated the law correctly for determining the state of the art. The Federal Court of Appeal in *Ciba* at paras 60, 62, confirmed that Apotex can choose the prior art elements that make the 422 Patent obvious as long as they were publically available prior to August 23, 2007. Although the 59 documents chosen by Apotex cannot be assumed to be common general knowledge without evidence of general acceptance by the notional POS, they all appear to be part of the prior art.

(i) State of the Art

[165] It is not necessary to list all 59 documents cited by Apotex as part of the prior art. The following briefly describe the important pieces of prior art and/or what they stand for.

a) Studies of AA in the 1990s

Barrie 1994, Potter 1995, and United States Patent 5,604,213 [213 Patent] issued in 1997 disclosed the use of AA for the treatment of hormone dependent cancers such as prostate cancer. AA was tested *in vitro* and in mice, which showed that AA did not inhibit the production of corticosterone and had less toxic effects than KC. The Potter 1995 article showed that AA had a slightly greater effect on 17,20 lyase activity than on 17α-hydroxylase activity, but this difference was not that significant. The 213 Patent is cited in the 422 Patent disclosure.

b) O'Donnell 2004 – a critical document in this case

i. O'Donnell 2004 was the only reported trial of AA treatment of prostate cancer in humans prior to 2007. The introduction of the O'Donnell 2004 article explains that prior studies had shown that residual androgens from the adrenal glands provided an important alternative source of testosterone for surgically or medically castrated prostate cancer patients. It also indicates that KC and AG had been evaluated as adrenal androgen inhibitors, but although promising, they were relatively unselective inhibitors. The observed effects of KC and AG supported research to find a more selective inhibitor of the CYP 17 enzyme – like AA.

ii. The O'Donnell 2004 trials were designed to assess the dose of AA that would suppress testosterone levels in castrate and non-castrate patients and obtain safety, pharmacokinetic, and hormonal data. There were three Phase I trials reported in O'Donnell 2004. Study A was a single dose study of surgically or medically castrated men. Study B was a single dose study in non-castrate men. Study C was a multi-dose study over 12 days in non-castrate males. Cohorts within each study received different dosage levels.

iii. The studies showed that AA could reduce testosterone levels in castrate and non-castrate males below castrate levels, which supported the proposed mechanism of action of the drug on testosterone levels. The study did not evaluate the effect of AA on prostate cancer itself and O'Donnell 2004 reported no evidence of efficacy. The patients in the studies had asymptomatic prostate cancer and therefore could not report any effect of the treatment on symptoms.

iv. The O'Donnell studies also showed that AA "was very well-tolerated and no serious adverse events attributable to treatment were recorded", only mild side effects were observed. None of the patients were allowed to take concomitant steroids. Baseline cortisol levels stayed within the normal range. One patient's cortisol dropped in Study A, but this was not thought to be related to AA as it happened on the first day of the trial. In Study C, the multiple dose branch, patients had a lower cortisol response on Day 11 when given a Synacthen test, which simulates a stress response. This was not considered to be a significant suppression of cortisol and therefore was not a major concern. In addition, in Study C, the three patients given the highest dose of AA (800 mg) had lower evening cortisol levels, but their other assessments remained normal.

v. In the discussion section of O'Donnell, the authors concluded that AA suppressed testosterone. They also concluded that a dose of at least 800 mg was required to maintain testosterone suppression and that higher doses may be required. The study indicated that any inhibition of 17α-hydroxylase activity by AA treatment was compensated by cortisol

feedback mechanisms. This compensation did not prevent inhibition of the 17,20-lyase activity, which prevented the synthesis of adrenal androgens.

vi. The authors concluded that although baseline cortisol levels remained normal, the abnormal response to the Synacthen test was not unexpected as some impact on adrenal reserve was predictable from the steroid synthesis pathway.

vii. The researchers did not conclude that AA treatment required co-administration with a glucocorticoid but concluded that further study was needed to determine whether AA treatment required any type of glucocorticoid therapy. The researchers indicated that AA treatment could require glucocorticoid therapy continuously through treatment, only when showing symptoms or at times of stress, or potentially would not require glucocorticoid therapy at all. Judson testified that if glucocorticoid was required at times of stress this would have meant that patients would be given a warning card with emergency hydrocortisone tablets to be taken in times of infection or trauma. The researchers also recommended that in the event of extreme physiological stress, AA treatment might be discontinued. O'Donnell 2004 noted that hydrocortisone was commonly used for glucocorticoid replacement therapy with KC or AG treatment. However, the article also stated that KC and AG treatment without glucocorticoids had been shown to be safe.

[166] The trials were completed in 1999. The article was not published until 2004. According to Judson, this was because the authors were met with scepticism as expressed in a letter referred to earlier. In addition, Judson stated that finding a commercial partner for developing AA treatment became difficult after Boehringer Ingelheim stopped its involvement. Having considered the letter, like Nam, I cannot find the scepticism alleged.

[167] Based on O'Donnell 2004, I find that a POS would see AA as a promising, but as yet unproven, secondary hormonal treatment for prostate cancer because of its ability to lower residual testosterone levels with fewer side effects than KC. The POS would interpret O'Donnell 2004 as indicating that AA likely inhibits both activities of CYP17, and therefore would expect AA to potentially cause lower cortisol levels.

However, the POS would not know whether these reductions in cortisol would likely require glucocorticoids to be taken concomitantly with AA as there were no clinical manifestations of symptoms.

[168] These conclusions generally favour Nam's interpretation of the article over Rettig and Auchus. Rettig and Auchus would have found that AA was only known to inhibit the 17,20-lyase activity of CYP17. O'Donnell 2004 and the review article, Attard 2005, indicate that both activities are affected, but that feedback mechanisms might compensate for any decrease in cortisol. I do not accept Nam's conclusion that a POS would expect glucocorticoid replacement to be necessary with AA treatment given that O'Donnell 2004 as well Attard 2005 indicated that researchers should monitor for glucocorticoid insufficiency rather than provide glucocorticoid replacement therapy.

(ii) Prior Art on the Anti-Cancer Effect of Glucocorticoids

[169] I have concluded that glucocorticoids, and specifically PN, were known as of 2007 to have modest short-term anti-cancer effect, but that the mechanism of the anti-cancer effects were unknown. Nam cited the following studies as showing that PN was already known as an anti-cancer agent in the prior art: Tannock 1989, Sartor 1998, Fossa 2001, Berry 2002, Harris 2002, Small 2004, Lam 2006, and Yano 2006. Rettig critiqued the conclusions of each of these studies for their study design and their failure to show survival benefit.

[170] Tannock 1989 examined the ability of PN to suppress adrenal androgens in a chart review of nine men who had previously been treated with primary hormone therapy for their prostate

cancer. The study measured pain and quality of life and also found that PN could lower adrenal androgen levels. It did not measure any anti-cancer effects or survival benefit.

[171] Sartor 1998 studied the effects of PN on PSA levels in CRPC patients. It observed a modest average PSA decline of 33% in a study of 29 patients with only about 2.8 months average progression-free survival. The study could not determine why PN caused a PSA decline. Rettig noted that the author of this study as of 2007 had concluded that glucocorticoids had not been shown to have a survival benefit.

[172] Fossa 2001 compared the effects of PN and a non-steroid anti-androgen. It noted that PN was known to suppress adrenal androgens. The study observed a similar effect from both drugs but found that PN resulted in greater quality of life. Rettig did not interpret this study as showing a potential for PN to act as an anti-cancer agent.

[173] Berry 2002 compared the effectiveness of PN and a chemotherapy drug with PN alone. The study concluded that although the combination of chemotherapy and PN was more effective, PN alone could also be useful in treating some patients with CRPC because of its observed effects on PSA levels. Rettig did not find that this study indicated that PN was useful in treating CRPC because no survival benefit was shown.

[174] Harris 2002 and Small 2004 did not study PN, but instead examined the combination of hydrocortisone and KC. The studies attributed some observed anti-cancer effect to hydrocortisone. Hydrocortisone was primarily added to KC to deal with side effects.

[175] Lam 2006, a review article, noted that glucocorticoids may have modest anti-cancer activity, although the best dosage or type of corticosteroid was unknown at the time.

[176] Yano 2006 studied the impact of dexamethasone on prostate cancer cell growth *in vitro* and *in vivo*. It concluded that observed anti-cancer effects in glucocorticoids were likely related to effects on tumour blood vessel growth and direct impacts on androgen receptors. The paper suggested combining glucocorticoids with anti-cancer agents, such as docetaxel (cytotoxic chemotherapy agent).

[177] Based on this prior art, I have concluded that the POS would know that glucocorticoids, including PN, could have anti-cancer effects, although the mechanism of the anti-cancer effect was not fully known. The POS would also know that glucocorticoids had been proposed to be used in combination with cytotoxic chemotherapy drugs and KC. Its use with KC had mostly been to treat side effects, but was also understood to potentially contribute to an anti-cancer effect.

(iii) Differences between the SOA and the Invention

[178] As a result of a comparison of SOA and the invention, I find the following differences between the two:

- AA was not known to effectively treat prostate cancer in 2007, although it was understood as a likely prostate cancer treatment in the prior art. No PSA response, tumour response, or survival benefit had been observed in humans. Further

clinical study as a potential prostate cancer treatment was supported by the prior art.

- Adrenal insufficiency and mineralocorticoid excess had not been observed as side effects of AA treatment. A POS reading O'Donnell 2004 would interpret the article as suggesting that AA needed to be studied further to determine whether treatment with glucocorticoids was required.
- PN had not been shown to have a survival benefit when administered alone to treat prostate cancer nor was there a well-understood mechanism about how PN might have an anti-cancer effect. However, PN was understood in the prior art to have moderate short term anti-cancer activity. Prior art, such as Yano 2006, had suggested that glucocorticoids may enhance the therapeutic effect of anti-cancer agents such as docetaxel.
- The key difference between the state of the art and the inventive concept was that AA and glucocorticoids, including PN, had not been combined to treat prostate cancer. There was no prior art put forward which suggested that the effectiveness of AA in treating cancer might be increased if used in combination with another drug. No prior art had proposed a hypothesis where glucocorticoids might prevent the development of resistance to treatment with AA.

(d) *Step 4: Obviousness/Degree of Invention*

[179] Given the identified gaps between the state of the art and the inventive concept, the POS would have to be able to bridge the gaps using their common general knowledge and information

available to them in a reasonable diligent search for the invention to be obvious. I conclude that the invention would not be obvious to the POS.

[180] The inventive concept in the 422 Patent requires not only the combination of AA and PN, but the combination for the purpose of treating prostate cancer, where each drug contributes to an anti-cancer effect. The experts agreed that neither drug in the combination was claimed in the Patent to treat the side effects caused by the other drug. Apotex's arguments on non-infringement and ineligibility of the 422 Patent are based entirely on this difference between the invention as claimed and the proposed use of PN to only treat side effects caused by AA.

[181] To come to the inventive concept, the POS would have to determine that AA should be further tested for the treatment of prostate cancer and then decide to combine AA with PN to treat prostate cancer.

(e) *Obviousness in the Prior Art and Common General Knowledge*

[182] In examining the prior art, I conclude that a POS interested in developing a secondary hormonal treatment for prostate cancer would likely choose to study AA, given its selectivity over KC and the likelihood that it had fewer side effects. A POS in 2007 would have likely understood that AA had good potential to treat prostate cancer.

[183] The mechanism of action proposed for AA to target the CYP17 enzyme would have been understood by the POS as being a mechanism of action that built off of the knowledge gained from use of KC and AG. O'Donnell 2004 acknowledges that it was the first study of CYP17

inhibitors in humans and showed that AA was well-tolerated. It appears likely that a POS would have chosen to look at AA as a CYP17 inhibitor to treat prostate cancer over the others.

[184] If the invention merely claimed the use of AA for the treatment of prostate cancer, this would likely be obvious in the prior art given O'Donnell 2004. However, there is no indication in the common general knowledge that the combination of AA and PN would have an anti-cancer effect.

[185] The prior art indicated that although PN had some observed anti-cancer effect, the mechanism of this effect was not known. Although prior art supported the combination of glucocorticoids with docetaxel and KC, the POS would not predict that AA and PN would have an anti-cancer effect when used together based solely on the knowledge that both drugs had individually shown some anti-cancer potential. A POS would not know that the two drugs would not, for example, cancel each other's effectiveness.

[186] In terms of side effects, a POS would understand that a selective CYP17 inhibitor like AA could potentially cause decreased cortisol levels from the prior art. A POS in 2007 would not be certain of what side effects this might cause, as side effects had not been shown in O'Donnell 2004, but they would be wary of the potential for adrenal insufficiency or mineralocorticoid excess to occur. The SOA showed that there was a potential for adrenal insufficiency or mineralocorticoid excess with AA given the emphasis put on monitoring for glucocorticoid insufficiency in O'Donnell 2004 and Attard 2005.

[187] Reading the prior art, the POS would understand that AA likely inhibits both activities of CYP17. I do not put much weight on the testimony of Auchus and Rettig who stated that the POS in 2007 would understand that AA preferentially inhibited the 17,20-lyase activity and would therefore not be expected to inhibit the 17α-hydroxylase activity.

[188] As admitted by Auchus, the *in vitro* tests of AA suggested a minimal difference in suppression between the two CYP17 activities. Further, the tests on mice cited by Auchus established that AA did not assess cortisol suppression because mice do not primarily rely on cortisol as their main glucocorticoid – unlike humans.

[189] O'Donnell 2004 as well as de Bono's description of the Cougar study design indicates that the POS would understand that there was a risk of decreased cortisol, and potentially adrenal insufficiency or mineralocorticoid excess, as a result of AA treatment.

[190] The Court notes that the endocrinology experts, Auchus and Prins, put forward arguments about how a POS would understand the likely side effects of AA by examining people with various types of congenital disorders related to the CYP17 enzyme. I did not find that evidence very informative given that I did not find that the POS would likely consult an endocrinologist and the experts agreed that CYP17 disorders vary significantly in terms of their effects. In addition, these effects were observed over a lifetime of having CYP17 inhibition, which would not be directly comparable to treatment for CRPC, which usually occurs in older men.

[191] As the experts agreed, KC, AG, and AA all hindered adrenal steroid production, but KC and AG inhibited the production of corticosterone as well as cortisol while AA would not inhibit corticosterone production. Therefore, I have concluded the POS would not assume that the same side effects observed with KC and AG treatment would apply to AA.

[192] I have concluded that the prior art had not established the existence of any side effects from AA, but the POS would be wary of potential effects given the slight cortisol responses observed in the short-term response in O'Donnell 2004. Given this uncertainty about the side effects of AA, it would not be obvious to combine AA with a glucocorticoid merely to prevent the possibility of yet-to-be observed side effects.

[193] Therefore, I have concluded that Apotex's allegation of obviousness is not justified.

(f) *Obvious to Try Consideration*

[194] An "obvious to try" test is warranted here, as this would be the type of pharmaceutical case referred to in *Sanofi* at paras 68-71 where advances are made through experimentation and a number of interrelated variables may affect the desired result.

[195] The Court therefore also has to consider whether the combination of AA and PN was more or less self-evident that it ought to work, by examining the extent, nature and amount of effort required to achieve the invention, motive in the prior art to find the solution the patent addresses, and the actual course of conduct of the inventors: *Sanofi, AstraZeneca Canada Inc v*

Mylan Pharmaceuticals ULC, 2017 FC 142 at paras 41-42, 145 CPR (4th) 371 [*Naproxen-Esomeprazole*].

I have considered the effort required to achieve the invention and the actual course of conduct of the inventors together.

[196] The combination of AA and PN to treat prostate cancer was not obvious to try. It was not more or less self-evident that AA and PN would both contribute to an anti-cancer effect when used together. The combination of AA and PN was one of a small number of possible solutions to developing an effective secondary hormonal therapy. The use of AA and PN together to treat prostate cancer was not known or predicted in any prior art.

[197] It was also not self-evident to combine AA and PN to treat the side effects of AA since side effects of AA were not known at the time. A POS might have predicted that AA could cause decreased cortisol levels, but the POS would not necessarily predict that the decline in cortisol levels would require glucocorticoid replacement.

[198] As regards extent, nature and amount of effort, the parties seem to either exaggerate or minimize the effort, as suits their position. However, AA was being researched and PN was being used in end-stage prostate cancer treatments. As such, they could not, as Janssen suggests, be considered “unsuccessful” drugs.

[199] However, the Cougar trials described by de Bono do not merely describe “routine” tests. For example, de Bono’s plan for an extension study where dexamethasone and AA would be

combined after patients developed resistance to AA, does not demonstrate a routine test where the inventors were only treating patients with glucocorticoids to address side effects. The inventors did not start out by treating patients with a combination of AA and glucocorticoids, instead they started with AA and then added dexamethasone according to the extension study. The inventors separated the extension study from the treatment of any side effects. The potential for side effects was addressed by giving patients emergency packets of hydrocortisone, rather than giving glucocorticoids concomitantly.

[200] The evidence suggests that there was and would be considerable effort required and hence contrary to the "obvious to try" principles.

[201] I accept that the POS would be highly motivated to develop secondary hormonal therapies, and specifically to test the effectiveness of AA as a prostate cancer treatment. O'Donnell 2004 and following review articles refer to the need for further tests and confirm the potential of AA as a treatment for mCRPC.

[202] In conclusion, I would find there was likely motivation to test the effectiveness of AA as a prostate cancer treatment, but I would not find that it was self-evident to combine AA and PN to try to treat prostate cancer. Although the use of PN with AA may have even been seen as "worth trying" in order to prevent theorized side effects, that is insufficient unless the invention was more or less self-evident: as held in *Naproxen-Esomeprazole* at para 163, citing *Alcon Canada Inc v Cobalt Pharmaceuticals Co*, 2014 FC 462 at para 129, 454 FTR 265.

[203] I have found that the allegation that the inventive concept in the 422 Patent is obvious is not justified. Whether something is "obvious to try" is just one consideration when determining whether there was a degree of invention required to bridge the differences between the prior art and inventive concept. Overall, I would find that some inventive ingenuity was required to combine AA and PN to treat prostate cancer and that the obvious to try principle has not been made out.

F. *Inutility*

[204] The test for utility is set out in *AstraZeneca Canada Inc v Apotex Inc*, 2017 SCC 36 at para 54, [2017] 1 SCR 943 [*AstraZeneca*]:

1. The Court must identify the subject matter of the invention; and
2. The Court must ask whether the subject matter is useful, based on whether it is capable of a practical purpose.

[205] Janssen argues that the utility of the Asserted Claims was demonstrated as of August 23, 2007, and that the Asserted Claims have utility in fact.

[206] As stated by the Supreme Court of Canada in *AstraZeneca* at para 55, Janssen must only establish that there was a "scintilla of utility" related to the subject matter of the invention as of the Filing Date either through demonstration or sound prediction.

[207] The subject matter of the Asserted Claims is the use of therapeutically effective amounts of AA and PN for the treatment of prostate cancer, refractory prostate cancer, and refractory prostate cancer that has been treated with at least one anti-cancer agent.

[208] Janssen argues that utility was demonstrated through the four Cougar trials and in the conference poster published by Cougar. Data from the trials showed that one patient experienced a drop in PSA after receiving a combination of AA and dexamethasone compared to levels with each drug alone. Other data showed tumour reduction with AA alone and six patients with mCRPC experienced drops in PSA after receiving combined AA and PN.

[209] Janssen also argues that the allegation that the invention in the 422 Patent lacks utility in fact is not justified because Apotex has not shown evidence. In addition, Janssen has cited a number of studies published after the Filing that confirmed that the invention was useful for treating prostate cancer.

[210] Apotex argues that the utility of the subject matter of the 422 Patent as claimed was not demonstrated or soundly predicted as of the Filing Date. Apotex agrees that the test for utility is set out in *Astrazeneca* at paras 49-56 and the subject matter of the patent must be capable of an actual relevant use with some useful objective. Apotex also characterizes the subject matter of the Asserted Claims similarly to Janssen's characterization.

[211] Apotex's position is that the Cougar trials did not demonstrate utility because dexamethasone was used, not PN. The reference to six patients ignored data from the other 16 in

the study. Apotex also challenges both Nam and Rettig's expert evidence because they applied the wrong test for utility.

Further, Apotex argues that the utility of the Patent was not soundly predicted because no data or reference to data or studies was disclosed in the Patent.

[212] In my view, Janssen has likely demonstrated utility in its Patent based on the results of the two Cougar trials prior to August 23, 2007. It has not made out its position on sound prediction because the Patent does not provide a factual basis or anticipated line of reasoning.

[213] The test for demonstrated utility is set out in *AstraZeneca* at para 54. First, the Court must determine the subject matter of the invention as identified by claims construction. Second, the Court must ask whether the subject matter is useful, meaning capable of a practical purpose. The element that was not mentioned by Apotex, nor seemingly appreciated by Apotex's expert, Nam, was that only a "scintilla of utility" must be established by demonstration or sound prediction as of the Filing Date (see *AstraZeneca* at para 55).

[214] The subject matter of the invention is the combination of therapeutically effective amounts of AA and PN to treat prostate cancer. The results of the COU-AA-001 and COU-AA-004 have to be interpreted in the context of all of the test results, unless one test conclusively proves that the compound had no utility: *Teva Canada Ltd v Novartis AG*, 2013 FC 141 at paras 215-216, 428 FTR 1.

[215] Nam and Rettig both agreed that, as of August 23, 2007, COU-AA-001 showed that AA was effective in treating prostate cancer alone by reducing tumour size and causing regression of bone disease. They differed as to whether either Cougar study could demonstrate that the combination of AA and PN was useful in the treatment of prostate cancer.

[216] I agree with Nam that on its own, COU-AA-001 could not demonstrate the utility of the Asserted Claims. As of August 23, 2007, the inventors only had the results from one patient who had responded to a combination of a dexamethasone and AA after his prostate cancer advanced with AA and dexamethasone alone. This supported the Asserted Claims, and provided a factual basis for de Bono's hypothesis, but would not show utility by itself.

[217] I do not put much weight on Apotex's position that COU-AA-001 tested dexamethasone and the Asserted Claims are for PN as the glucocorticoid to be used in combination with AA. Even Nam acknowledged that the equivalent dosage for dexamethasone and PN was already known. De Bono's hypothesis for the effectiveness of AA with a glucocorticoid to treat prostate cancer was based on the effects of glucocorticoids as a class rather than PN or dexamethasone specifically.

[218] The preliminary results of COU-AA-004 did demonstrate utility of the combination in treating prostate cancer. Nam admitted that the results of COU-AA-004 were "encouraging" and that the PSA responses indicated that the treatment resulted in biologic activity towards prostate cancer. The fact that six patients out of 22 over a period of only two months had experienced a drop of PSA levels of greater than 50% shows the utility of the combination of AA and PN.

[219] These results support that the combination of AA and PN had utility in the treatment of prostate cancer. However, the preliminary results of COU-AA-004 did not show that the combination of AA and PN had any greater effect than PN on its own or AA on its own.

[220] The main issue is whether these studies are enough to show that the combination of drugs was useful, as neither study has a clear comparison that would allow a person to determine that the combination was more effective than either drug taken alone.

[221] However, I have concluded that when considered in the context of the COU-AA-001 study as well as previous studies of the modest anti-cancer effects of PN, they provide evidence of a scintilla of utility of the combination of AA and PN over the anti-cancer effects of AA or PN on their own.

[222] As indicated earlier, I agree with Apotex that the utility of the Asserted Claims were likely not soundly predicted because the factual basis and line of reasoning were not disclosed in the 422 Patent. The Supreme Court of Canada stated in *Apotex Inc v Wellcome Foundation Ltd*, 2002 SCC 77 at para 70, [2002] 4 SCR 153, that sound prediction requires a factual basis, line of reasoning, and disclosure of the prediction in the patent. Although some commentary has suggested the Supreme Court of Canada may have overturned this statement, the Federal Court of Appeal in *Bell Helicopter Textron Canada Limitée v Eurocopter, société par actions simplifiée*, 2013 FCA 219 at paras 152-155, 120 CPR (4th) 394, confirmed that where the factual basis and line of reasoning are based on data that is not part of the common general knowledge, then disclosure is likely required to support sound prediction.

[223] Without a disclosure requirement, Janssen would likely be able to establish that the claims were soundly predicted. The study protocol of the COU-AA-001 study clearly articulated de Bono's factual basis and line of reasoning for why the combination of AA with a glucocorticoid would prevent a patient from developing resistance to AA treatment and contribute to the anti-cancer effect. However, no part of de Bono's hypothesis or the Cougar studies were disclosed in the 422 Patent and therefore Janssen cannot rely on sound prediction.

[224] As stated earlier, Apotex's allegation of inutility is not justified because it could not make out utility in fact.

G. *Infringement*

[225] The test for infringement by inducement is set out in *Corlac Inc v Weatherford Canada Ltd*, 2011 FCA 228 at para 162, 204 ACWS (3d) 888 [*Weatherford*]:

1. The act of infringement will be completed by the direct infringer;
2. The acts of infringement were influenced by the acts of the "infringer" to the point that, without their influence, the direct infringement would not have taken place; and
3. The "infringer" must know that their influence will result in the completion of the act of infringement.

[226] Janssen submits that as Apotex will offer a product for sale with instructions that enable the public to infringe the claims of a patent, Apotex is liable for inducing infringement.

[227] Janssen argues that the evidence of infringement can be found by examining the proposed Product Monograph for APO-ABIRATERONE. The APO-ABIRATERONE Product

Monograph and Janssen's Product Monograph for ZYTIGA have essentially the same Indications and Clinical Use section; both products indicate the use of AA and PN for the treatment of mCRPC. The studies used to support the indication provide evidence of the safety and efficacy of using AA and PN in combination to treat prostate cancer. Physicians will prescribe APO-ABIRATERONE and PN in combination in the recommended doses because they currently prescribe ZYTIGA in these dosages and because both product monographs have the same indication and recommended dosage.

[228] Although Apotex has noted in the Warnings and Precautions section of the APO-ABIRATERONE Product Monograph that PN is used for palliation to address adverse events, rather than to treat prostate cancer, this does not negate the Indications and Clinical Use which directs the use of AA and PN to treat prostate cancer.

[229] Apotex's position that its APO-ABIRATERONE product will not induce infringement of the 422 Patent because an essential element of the 422 Patent is missing from the indications on the APO-ABIRATERONE Product Monograph. Infringement requires that the alleged infringer takes all essential elements of a claim, as infringement is an act that interferes with the full enjoyment of the monopoly granted to a patentee: citing *Free World* at para 64; *Monsanto Canada Inc v Schmeiser*, 2004 SCC 34 at paras 34-35, [2004] 1 SCR 902.

[230] Apotex emphasizes that Janssen must show that but for Apotex's activities, the direct infringement would not take place. If Apotex is not seeking for its product to be indicated for the claimed use and the evidence fails to establish that the generic drug producer will induce others

to prescribe or use the generic product for that claim's use, then there is no inducement to infringe.

Infringement by inducement cannot be established merely from a reference to the claimed use in the product monograph in the course of explaining contraindications or drug interactions, or as part of a list of scientific references: *Sanofi-Aventis Canada Inc v Novopharm Ltd*, 2007 FCA 167 at para 11, 59 CPR (4th) 24 [*Ramipril*].

[231] Relying on *Bristol-Myers Squibb Canada v Apotex Inc*, 2017 FC 1061 at para 33, 286 ACWS (3d) 732, Apotex contends that inducement will only be found where the use of the drug overlaps with the use claimed in the Patent. Inducement must not be interpreted to give the patent holder a complete monopoly over the drug for uses beyond what was indicated in the Patent. This is particularly the case where a drug has more than one use – in this case cancer treatment and palliative/side effects reduction.

[232] Despite the high bar to meet the test for infringement by inducement, I have concluded that Apotex's allegation of non-infringement of the 422 Patent is not justified. This is a clear case where Apotex intends to use the same drugs in the same amounts and for the same overall purposes of the Patent.

[233] The parties agree that the test for infringement by inducement is set out in *Weatherford* at para 162, which is a difficult test to meet. I note that Janssen has in parts of its argument compared the ZYTIGA and APO-ABIRATERONE Product Monographs, which is incorrect. The question is whether Apotex will induce infringement of the Asserted Claims of the 422

Patent, not whether the APO-ABIRATERONE product is similar to Janssen's ZYTIGA product. ZYTIGA overlaps sufficiently with the 422 Patent claims, as discussed under the history issue.

[234] Of the three parts of the *Weatherford* test, the main issue here is whether the direct infringement of the 422 Patent would have not occurred, but for the actions of Apotex in influencing the direct infringer. In addition, Apotex must induce infringement of all essential elements of the Asserted Claims.

[235] The Court can make reasonable inferences from the product monograph, evidence relating to the dosage form of APO-ABIRATERONE, or its labelling and marketing to determine infringement by inducement: *Ramipril* at para 11. Merely referring to the patented use when explaining contraindications or as part of a list of scientific references is not sufficient to establish inducement.

[236] Although the scientific references in the product monograph also include references to the uses claimed in the 422 Patent, the content of the APO-ABIRATERONE Product Monograph itself provides enough information to conclude that Apotex will likely induce infringement of the 422 Patent.

[237] Janssen's experts all emphasized the first section, "Indications and Clinical Use", of the APO-ABIRATERONE Product Monograph, which states that APO-ABIRATERONE is indicated in combination with PN for the treatment of mCRPC in patients. According to Dr. So,

a physician reading this section would understand that the combination is for the treatment of prostate cancer, meaning having an anti-cancer effect.

[238] Nam emphasized that this indication did not mention a "therapeutically effective amount" of PN, which he interpreted as meaning that PN was not indicated as having an anti-cancer effect in the APO-ABIRATERONE Product Monograph. He also noted that clinicians would not look at the Indications and Clinical Use section, but rather would mainly look at the Warnings and Precautions section, which describes the use of glucocorticoids to treat the side effects of AA, because of the possibility of using drugs off-label.

[239] I do not accept that the first section of a product monograph, which describes the indication of a drug and how it is to be used, would not be of importance to a physician when determining how to use a new drug. In fact, the focus in examining infringement by inducement is whether Apotex is seeking its product to be indicated for the claimed use: *Ramipril* at para 11.

[240] Unless the word "treatment" in the product monograph is intended to include the management of side effects unlike the word "treatment" in the 422 Patent, the indication in the product monograph is almost exactly the same as the use claimed in the Asserted Claims. There is no evidence that "treatment" is used to connote management of side effects.

[241] The words "therapeutically effective amount of prednisone" are not in the product monograph, but neither are the words "therapeutically effective amount" of APO-

ABIRATERONE. One cannot take Apotex to be arguing that it is indicating a use of APO-ABIRATERONE in an amount that is not effective for treating prostate cancer.

[242] Importantly, although the words "therapeutically effective amount" are not used, the recommended daily dosage for APO-ABIRATERONE is 1000 mg per day with 10 mg of PN. This is the same dosage of AA in Claim 6 combined with an amount of PN within the recommended range in paragraph 73 of the 422 Patent (10 to 250 mg per day of PN). In the context of the 422 Patent as a whole, the amount of 10 mg is claimed as a "therapeutically effective amount" of PN. Apotex has not provided evidence that its dosage of PN is not a "therapeutically effective amount" or that PN is acting solely in some other capacity.

[243] In contrast to the cases cited by Apotex, this is not a case where "off-label" use might infringe the 422 Patent claims. Instead, the indicated use of APO-ABIRATERONE and PN is for the treatment of mCRPC, which is the same use as the Asserted Claims.

[244] Apotex has admitted in its written representations that PN has an anti-cancer effect. Therefore, it is unavoidable that Apotex will be inducing infringement by directing the use of APO-ABIRATERONE and PN in its product monograph for the treatment of mCRPC. The effects of PN are not separable – if it has both the ability to treat side effects from AA and have an anti-cancer effect then it will do both of those things in the body.

[245] This is not a case where Janssen is attempting to expand its monopoly broadly over any use of AA, rather the disorder targeted, the dosages, and the combination of drugs are the same

as the Asserted Claims. This is also not a case where Apotex alleges that there is overbreadth in the Claims particularly as to dosages of PN.

[246] Therefore, by directing physicians to prescribe APO-ABIRATERONE and PN in combination for the treatment of mCRPC, Apotex will be inducing them to infringe the 422 Patent.

H. *Listing Eligibility*

[247] The issue is whether the 422 Patent is eligible to ground a prohibition order under the Regulations. Janssen alleges that Apotex is not able to raise the issue of whether the Asserted Claims are irrelevant or improperly listed because Apotex did not raise this allegation in a motion under subsection 6(5) of the Regulations as required.

[248] Janssen also argues that even if the Court can consider this issue without the motion, unlike with allegations of invalidity, Apotex has the burden to establish that the 422 Patent is not properly listed. Apotex has engaged the Regulations by directly comparing its product to ZYTIGA. The 422 Patent is properly listed and relevant to ZYTIGA. ZYTIGA is indicated to be used in combination with the drug PN for the treatment of prostate cancer, which is the same subject matter as the Asserted Claims.

[249] Apotex argues that it was not required to bring a motion under subsection 6(5) of the Regulations in order to raise issues at this hearing regarding the eligibility for listing of the 422 Patent.

[250] Apotex alleges that any claim in the 422 Patent that does not relate to the use of ZYTIGA is not relevant and is ineligible to ground a prohibition order under the Regulations according to subsection 4(2) of the Regulations. This requires a high degree of precise and specific matching between the patent claims and ZYTIGA's ingredients, its use, and dosage for which the Notice of Compliance has been issued: *ViiV Healthcare ULC v Teva Canada Ltd*, 2014 FC 893 at para 48, 464 FTR 66; *Gilead Sciences Canada Inc v Canada (Minister of Health)*, 2012 FCA 254 at paras 37, 40, 222 ACWS (3d) 500.

[251] Apotex states that ZYTIGA, like APO-ABIRATERONE, is indicated for use with PN for the treatment of mCRPC where the role of PN is to mitigate the side effects of AA. This is how the use of PN with ZYTIGA is explained in the ZYTIGA Product Monograph and through its marketing, US Food and Drug Administration documents, and presentations by urologists on behalf of Janssen. In contrast, the 422 Patent relates to the use of PN as an anti-cancer agent in combination with AA. This means that the use of PN with ZYTIGA and under the 422 Patent claims do not match, making the 422 Patent ineligible for listing under s 4(2) of the Regulations.

[252] Given the Court's earlier findings, this issue may be academic. Apotex's basic contention is that there is no nexus between ZYTIGA and the 422 Patent and therefore the Patent cannot be listed because PN's role is to deal with side effects, not cancer treatment.

[253] The procedural issue is whether the matter of patent listing can be raised in the NOC or whether a motion must be brought to include the issue in these proceedings.

[254] In *Bayer Inc v Apotex Inc*, 2014 FC 436, 454 FTR 48, Justice Hughes held that procedurally the matter of listing could be dealt with by a motion or in the NOC proceeding itself. Other judges of this Court have said the same.

[255] NOC proceedings are cumbersome enough and absent a clear bar to proceeding in alternate ways, I am of the view, consistent with Rules 3 and 4, that the matter can be raised either way.

[256] The parties did not make significant argument on the substantive issue of listing. In considering the findings already made which show the nexus between ZYTIGA and the Patent, while the approved role of PN is primarily to manage side effects, PN was understood to contribute to the treatment of the cancer itself.

[257] Section 4(2.1)(c) of the Regulations only requires one of the uses claimed in the submissions to match up with the use claimed in a patent.

[258] The ZYTIGA Product Monograph emphasizes the role of PN in combination with AA primarily to alleviate side effects but there is acceptance of contribution to anti-cancer effects.

[259] The 422 Patent is eligible to ground a prohibition under the NOC Regulations.

V. CONCLUSION

[260] For all these reasons, the Court will issue an order to the Minister of Health prohibiting the issuance of a Notice of Compliance to Apotex Inc for its proposed abiraterone acetate product [APO-ABIRATERONE] until the expiry of Canadian Patent No 2,661,422.

[261] Janssen Inc shall have its costs at the usual level.

"Michael L. Phelan"
Judge

Ottawa, Ontario
October 29, 2019

FEDERAL COURT

SOLICITORS OF RECORD

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