Federal Court  Cour fédérale

Date: 20210114

Dockets: T-84-19
T-978-19
T-182-19
T-1893-19

Citation: 2021 FC 7

Docket: T-84-19

BETWEEN:

JANSSEN INC, JANSSEN ONCOLOGY, INC AND BTG INTERNATIONAL LTD

Plaintiffs

and

APOTEX INC

Defendant

Docket: T-978-19

AND BETWEEN:

JANSSEN INC, JANSSEN ONCOLOGY, INC AND BTG INTERNATIONAL LTD

Plaintiffs

and

DR REDDY'S LABORATORIES LTD AND DR REDDY'S LABORATORIES, INC

Defendants

Dockets: T-182-19
T-1893-19

AND BETWEEN:

JANSSEN INC, JANSSEN ONCOLOGY, INC AND BTG INTERNATIONAL LTD

Plaintiffs

and

PHARMASCIENCE INC

Defendant

PUBLIC REASONS FOR JUDGMENT
(Identical to the Confidential Reasons for Judgment issued on January 6, 2021)

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PHELAN J.

I. Introduction

[1] This is a patent infringement action pursuant to s 6(1) of the *Patented Medicines (Notice of Compliance) Regulations*, SOR/93-133 [NOC Regulations].

[2] These are the Reasons in respect of the Judgments issued January 8, 2021, dismissing the Plaintiffs' action. The trial of these actions covered five weeks concluding at the end of November 2020. The statutory stay under the NOC Regulations expires January 9, 2021, and a decision was necessary before that date.

[3] This Court decided a similar NOC proceeding under the previous NOC Regulations where the dispute was conducted as an application. In that proceeding the Court granted the Plaintiffs' application for a prohibition against granting a Notice of Compliance to one of the Defendant's – Apotex Inc – for its proposed abiraterone acetate [AA] product (*Janssen Inc v Apotex Inc*, 2019 FC 1355). That judgment is under appeal. Those proceedings and judgment are referred to as the "2019 NOC".

[4] The Patent at issue is a combination method and treatment for cancer, principally prostate cancer, by combining a 17α-hydroxylase/$C_{17,20}$–lyase inhibitor such as AA with an anti-cancer agent or a steroid, in this case prednisone [PN].

II. Procedural History

[5] That NOC application was one of the last, if not the last, under the old NOC Regulations. New NOC approvals were sought by the Defendants for their respective AA products [Products]. This resulted in the subject action by the Plaintiffs.

[6] The actions were against each Defendant individually but the trial was conducted as one action. It was led in large measure by Apotex and subject to limited specific aspects related to each Defendant, Apotex and its draft Product Monograph served as a notional surrogate for all Defendants. The cooperation and professionalism of counsel facilitated the orderly and complete hearing of this dispute in these difficult COVID-19 times and the use of Zoom technology.

[7] There were no issues raised with respect to any form of estoppel as between the 2019 NOC and this action. The parties treated the matter as an entirely new proceeding as does this Court.

[8] The old NOC application regime had been much criticized and was replaced. The new actions afforded the parties and the Court an opportunity to obtain further and better evidence by way of production and discovery and new submissions.

[9] The parties took advantage of these more complete procedural rights. They also advanced new and better evidence in such areas as biostatistics and endocrinology. Previous witnesses were open to examination on a more complete record resulting from the pre-trial discovery process.

[10] The Court has had the advantage of hearing directly from witnesses. It has had better evidence, current legal teachings and more focused argument.

[11] Therefore, unless specifically adopted from the 2019 NOC – as in the case of claim construction – the findings and comments in that decision are irrelevant to the trial. This new process is somewhat like the previous right to sue for relief despite the findings in a related NOC proceeding.

[12] Under this new action process, the Court (especially where the judge on the previous NOC is the same as on the trial) is required to approach the case afresh with "a mind willing to understand and be persuaded". The Court must come to the process with understanding but without conclusions.

III. Background

A. *Parties/Claim*

[13] Janssen Oncology, Inc [Janssen] and BTG International Ltd are the owners of Canadian Patent No. 2,661,442 [422 Patent or Patent]. The 422 Patent was issued from an application filed

on August 23, 2007 and published February 28, 2008 – the differences in dates have no impact in this case.

[14] When the Patent application was filed in 2007, the proposed patent described and claimed a large number of combinations of a CYP17 inhibitor – including AA – and one or more of a therapeutic agent including anti-cancer agents. At least one embodiment combined the inhibitor with PN as an antibiotic but in the embodiment in respect to anti-cancer agents, PN is not mentioned.

[15] In 2011, before the 422 Patent was issued, the Plaintiffs obtained approval for its AA formulation ZYTIGA to be administered with PN to treat side effects. It then filed revised claims with the Patent Office to claim the combination of AA and PN to treat cancer as specified in the Asserted Claims.

[16] Janssen alleges that the Defendants have or will infringe Claims 3, 6, 7, 14 and 15 [the Asserted Claims].

[17] These claims read:

> 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.

[18] The Defendants allege that each of the Asserted Claims is invalid. Apotex has also alleged in a counterclaim that the "Non Asserted" Claims are also invalid.

[19] The issue of invalidity is dispositive of the Plaintiffs' Statement of Claim. However, to facilitate appellate review (which the Court was advised the Plaintiffs would seek no matter the result), the Court has dealt with the Infringement issue as well.

B. *Overview*

[20] Prostate cancer, the uncontrolled growth of cells in the prostate gland, is the most commonly diagnosed cancer in men and the second leading cause of cancer-related deaths in men. While early prostate cancer may be treated or not and monitored, at some point the cancer may spread to other parts of the body – becoming metastatic cancer.

[21] Most men with metastatic prostate cancer are treated with androgen deprivation therapy [ADT] because the male sex hormones (androgens) specifically testosterone promote prostate cancer.

Since the 1940s the primary treatment for metastatic prostate cancer by ADT was through medical or surgical castration to suppress androgen production in the testes. Patients treated with ADT still had some residual androgens in their system because the adrenal gland produces 10% of circulating androgens in men.

[22] When the prostate cancer begins to progress after ADT, it is referred to as "castration-resistant prostate cancer" [CRPC] and if the cancer has metastasized, it is referred to as mCRPC.

[23] A standard measurement in the treatment of prostate cancer is "PSA" level – prostate-specific antigen (a protein produced in the prostate gland). It is used to detect prostate cancer and to indicate the response to prostate cancer treatments. The PSA response was used as a surrogate measurement for the effectiveness of prostate cancer treatment although not a perfect indicator of such – it did not indicate survival benefits. A surrogate for survival benefit was necessary because the only way to determine such benefit is for the patient to die.

The issues of PSA and survival benefits arose in this trial with several of the Plaintiffs' experts equating or measuring the usefulness of an anti-cancer drug against observed survival benefits rather than an anti-cancer effect as per the Patent.

[24] By August 2007 (the threshold date for this matter), a group of cytotoxic chemotherapy drugs called taxanes, and more specifically docetaxel (approved in 2004), showed a modest survival benefit in mCRPC patients. Its method of action was different from hormonal therapies like ADT.

[25] Docetaxel's survival benefit was a "new paradigm", as Dr. Nam explained, for the treatment of patients with mCRPC. However, there were significant side effects in many patients. A further major problem was that mCRPC patients stop responding to treatments with docetaxel which eventually leads to death.

[26] Before 2007, aminoglutethimide and ketoconazole were used in prostate cancer therapy but neither improved survival. They were understood to be non-specific inhibitors of adrenal steroid synthesis and had serious side effects, including glucocorticoid deficiency which sometimes required concomitant glucocorticoid use. Neither compound was said to cause mineralocorticoid excess (an area of debate) but as Dr. Bantle pointed out, even if mineralcorticoid levels remained normal, low levels of glucocorticoid had their own serious side effects.

[27] PN, a glucocorticoid, was used to palliate prostate cancer patients and alleviate side effects of treatment. It was an old drug – available since the 1950s. It was known to have some anti-cancer effects but how and how much was not known. PN did offer palliation, relief from side effects and some anti-cancer effects (sometimes called anti-tumour activity) but not an established survival benefit. PN had not been approved as an anti-cancer drug.

[28] As disclosed in the 422 Patient, CYP17 inhibitors, of which AA is one, had been shown to be useful in treating prostate cancer. AA was a newer drug than PN.

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

[30] Attached as Schedule A to these Reasons is a chart of the relevant pathways produced in Dr. Bantle's expert report and of considerable help to this Court.

C. *Witnesses*

(1) Fact Witnesses

[31] Dr. Johann de Bono, Regius Professor of Experimental Cancer Medicine in the U.K., is a prostate cancer researcher, physician and a named inventor of the 422 Patent.

[32] The Defendants attempted to discredit his inventorship; however, he was added as an inventor by Order of Justice Heneghan (*Janssen Oncology, Inc and BTG International Ltd v Canada (Attorney General)* (June 15, 2018), T-1495-17 (Federal Court)) and it is not for this Court to go behind that Order.

However, the Court is aware that Dr. de Bono's work was to develop a hypothesis which was not the patent eventually filed. He himself was surprised to learn of the 422 Patent.

[33] Dr. de Bono leads the Prostate Cancer Team at the Institute of Cancer Research [ICR] at the Royal Marsden Hospital.

He gave direct useful evidence as to the trials which led to the 422 Patent. He traced the process of his hypothesis that glucocorticoid supplementation could reverse resistance to AA by reducing the body's production of upstream adrenal steroids[1]. In that regard, while he used dexamethasone because it was available at ICR, as he admitted any glucocorticoid would do. PN was not then available in the UK.

[34] Dr. Gloria Lee, a physician and former Vice President of Clinical Research and Development at Cougar Biotechnology Inc [Cougar], the sponsor of the clinical trials that led to the 422 Patent. Her evidence gave context and details of the four (4) Cougar studies – COU-AA-001, 002, 003 and 004 as well as the 2008 Protocol Amendment.

[35] Dr. Robert Charnas was the Global Regulatory Leader at Cougar (now Janssen Oncology Inc) and was responsible for the regulatory submission for the ZYTIGA (the Plaintiffs' AA product) project. Like Dr. Lee, his evidence encompassed the Cougar Studies and the Protocol Amendment but also the two Phase II studies COU-AA-301 and 302 which compared the efficacy of the combination of PN and AA in mCRPC patients with PN and placebo.

(2) Expert Witnesses

[36] This case was largely driven by expert evidence. It is the Court's task to assess this difficult evidentiary field, both as a whole and individually with each expert.

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[1] ... hypothesis was directed to whether drug resistance could be reversed by administering dexamethasone to suppress ACTH and the 21-carbon steroids upstream of the CYP17 drug target in the steroid biosynthesis pathways. (Transcript, November 5, 2020, at p 380)

[37] There were areas of weakness, lack of clarity and other such issues with respect to most experts but the Court must assess credibility and weight against something less than perfection.

(a) *Janssen's Experts*

[38] Dr. Geoffrey Gotto is currently the Medical Director at the Clinic for Advanced Metastatic Prostate Cancer in Calgary and a Clinical Associate Professor at the University of Calgary. He was qualified as an expert in urologic oncology, including clinical matters involving the diagnosis and treatment of prostate cancer including surgery and prescribing of medical interventions. This expertise includes an understanding of prescribing decisions by Canadian urologists for the treatment of prostate cancer. His evidence in general covered details of the use made of a drug's product monograph, data supporting ZYTIGA's product monograph, the instructions to be taken from a product monograph, the Apotex and other Defendants' Product Monograph instructions to urologists, and a comparison of product monographs.

[39] Dr. Gotto was helpful in providing context and understanding of the drugs from an urologist's perspective. His involvement with Janssen, while not ideal in terms of objectivity, did not imperil his credibility. He was challenged in explaining the roles of AA and PN to the extent that product monographs spoke of PN in terms of side effects. Despite these statements, the product monograph in Dr. Reddy's indicated that PN is to be used to treat prostate cancer for its anti-cancer effects when used in combination with AA. His equivocating on PN's anti-cancer effects was unsatisfactory and suggested a protectiveness of the Plaintiffs and their position.

[40] Jane Costaris is the President of Regulatory Solutions Inc and was qualified as an expert in regulatory affairs and quality compliance for the pharmaceutical, natural health product, and medical device industries. She has expertise in federal and provincial regulatory submissions for drug and health products in Canada, including both new drug submissions and supplemental new drug submissions, as well as submissions for subsequent entry/generic products. In addition, she has expertise in preparing advertising/marketing materials for drug products in Canada. She gave general evidence on regulatory matters with Health Canada and specifics on the particular Product Monographs in issue in this litigation. Her evidence was generally uncontroversial.

[41] Dr. Matthew Rettig is a medical oncologist with 25 years' experience in prostate cancer and a key witness for the Plaintiffs. He was qualified as an expert in medical oncology, and in particular the diagnosis, treatment, and management of urologic cancers including the treatment of prostate cancer. This expertise includes: (a) the design, conduct, and interpretation of results from clinical trials from a clinician's perspective; (b) the use of agents in the treatment of prostate cancer, palliation of prostate cancer, and management of side effects associated with prostate cancer treatments; and (c) understanding prescribing decisions by medical oncologists for the treatment of prostate cancer.

[42] Dr. Rettig was involved on behalf of Janssen as a local co-investigator and principal investigator for clinical trials relating to AA and PN, particularly the 301 and 302 studies and principal investigator in the 004 study (one of the core subjects of this litigation). It was an unfortunate closeness to the subject of what should be an objective opinion. His evidence covered a broad range of topics from common general knowledge [CGK], the POS (person of

ordinary skill in the art), construction of words in the Patent, through to infringement. In summary, his opinion is that:

- arriving at the 422 Patent's claimed invention would have required inventiveness and would not have been obvious to a POS as of August 2007 – that it would not have been obvious to try the combination of AA and PN (or either agent alone) to treat cancer.
- utility of the subject matter is demonstrated by the data in the possession of the inventors prior to August 2007 but not disclosed in the Patent.
- the Asserted Claims cover the combination of AA and PN to treat prostate cancer. ZYTIGA is approved for this use.
- as of 2007 a POS would have been able to practice the Asserted Claims based on the teachings of the Patent and the CGK.
- a physician is not required or expected to use skill/judgment to put the subject matter into practice.

[43] Dr. Rettig's report was well constructed, clear but flawed. His evidence is to be contrasted with Dr. Nam and Dr. Lipton on behalf of the Defendants. In his non-core area of expertise, endocrinology, his comments can be contrasted with Dr. Bantle.

[44] Dr. Rettig's evidence was seriously undermined in cross-examination. It was not just questions of wording choices and nuance but he was required to concede and have struck or changed from his report major conclusions particularly as related to the "obviousness" issue in respect of aminoglutethimide's anti-cancer effects, the same in regard to ketoconazole, the

known requirement to have glucocorticoid replacement for aminoglutethimide and ketoconazole, and the role of PN for an anti-cancer effect. He made other major concessions in these important areas.

[45] Among the many reversals and clarifications of his report is that he was forced to admit that PN was known to have an anti-cancer effect; that aminoglutethimide was known to have anti-cancer treatment effects in prostate cancer; and that ketocconazole had an anti-cancer effect.

[46] His explanation for this changing of opinion from “not have an anti-cancer effect” to “have an anti-cancer effect” was that he had in mind known survival benefit not anti-cancer effect. This may be true in his mind but it is unsatisfactory given his evidence about the claims. Despite these revisions to his report, he maintained his opinion that it was not obvious to try to combine AA and PN as claimed because there was no motivation to do so. It is a tenuous opinion at best and not one on which the Court can rely.

[47] His utility analysis, while nevertheless helpful, was shaky because it proceeded on an error in understanding of the applicable law. He admitted to understanding that the criterion was “a scintilla of evidence of utility” rather than “a scintilla of utility”.

[48] I do not reject his report in whole and I generally accept his opinion in some areas of validity (e.g. utility) and in respect of infringement. However, I find in many areas of validity, particularly the obviousness analysis, that the Defendants’ relevant experts are more credible and where the two sides part, I generally accept the Defendants’ experts.

[49] Dr. Karla Ballman is the Chief of the Division of Biostatistics (a new field in this litigation) in the Department of Population Health Sciences at Weill Cornell Medical College. She was qualified as an expert in biostatistics, in particular cancer biostatistics. She has expertise in clinical trial design and analysis of clinical trial data and interpretation of results from a biostatistician's perspective, including mathematical modelling, statistics, probability, data analysis and experimental design.

[50] She provided useful and clear evidence on the relevance of biostatistics and the meaning which can be drawn from the Cougar studies and from such publications as Attard 2009, Danila 2010 and Reid 2010. Her evidence was confirmatory of PN's role as providing an anti-cancer effect in the combination of AA and PN for the treatment of prostate cancer.

[51] Dr. Ballman was prepared to make these conclusions in contrast to the Defendants' biostatistician, Dr. McKeague. She was required to make the assumption that dexamethasone and PN are members of the same class and behave similarly. While the Defendants criticize that assumption, she accepted it based on her considerable experience in the area of oncology. In that regard, Dr. Ballman's experience, in my view, allowed her to bring professional judgment to areas of uncertainty which others highly qualified in their specific field but not as experienced in oncology, could not. Her evidence was helpful and persuasive.

[52] Dr. Richard Auchus is a clinical endocrinologist, practising and researching steroid hormone synthesis for over 25 years. He was said to have extensive experience diagnosing and treating patients with adrenal conditions. He was qualified as an expert in clinical endocrinology

and research and clinical management of endocrinologic disorders involving steroidogenesis, including androgen synthesis and action. This expertise includes diagnosing and treating patients with congenital and non-congenital conditions involving changes in steroid hormone production, including adrenal insufficiency and disorders of mineralocorticoid production.

[53] Dr. Auchus disclosed his extensive involvement over the years for Cougar (now Janssen) including with respect to AA – whether to administer a glucocorticoid with AA, one of the central issues in this case. While this disclosure was made in this case, he did not disclose this level of involvement in the 2019 NOC where he was a witness. His direct and substantive involvement and relationship with a participant calls into question – at least on an objective view – whether he could provide the kind of unbiased opinion contemplated by the Code of Conduct for Expert Witnesses. The Court was not comfortable with this level of involvement and it affected the weight which could be given to his evidence.

[54] Dr. Auchus was of the view that a glucocorticoid did not have to be co-administered when AA is used. He drew a distinction between ketoconazole/aminoglutethimide and AA and called into question the teachings of O'Donnell 2004. He discounted the use and need for Synacthen tests. His principal points were undermined in cross-examination including that a glucocorticoid might have to be administered for other side effects. He had his theory, the correctness of which is not for resolution here, but his evidence of what a POS would know and do, was unconvincing.

[55] Dr. Auchus' evidence was almost completely at odds with Dr. Bantle on the key issues in this case. On many of these issues, the Court had to choose as between these witnesses. On the strength of Dr. Bantle's evidence in the contrast of the weakness of Dr. Auchus', this Court has relied more heavily on Dr. Bantle's evidence.

(b) *Defendants' Experts*

[56] Dr. Robert Nam is a professor of surgery at the University of Toronto, Head of the Genitourinary Cancer Program, Odette Cancer Centre as well as other relevant positions. He works in the fields of oncology and epidemiology maintaining a practice significantly focused on prostate cancer management. He was qualified as an expert in the field of urologic oncology and specifically the treatment of patients with prostate cancer (including advanced or metastatic prostate cancer), and clinical epidemiology of prostate cancer.

[57] Dr. Nam's evidence was wide ranging including the CGK of a POS noting that by August 2007, dexamethasone, hydrocortisone and PN were the most common glucocorticoids used in prostate cancer treatment. He addressed issues of PSA as a surrogate indicator of treatment effectiveness and PN as having an anti-cancer effect. He pointed the way in the analysis of obviousness (obvious to try) to the conclusion that the Asserted Claims were obvious. He reviewed the relevant literature and test results as part of forming his opinion.

[58] He also covered off other areas tangentially, such as biostatistics. The Court found his evidence helpful and persuasive where it was grounded in his main areas of experience and expertise. It was forceful when read in conjunction with Dr. Lipton's evidence. As contrasted

with Dr. Rettig, the Court put more reliance on Dr. Nam's evidence alone and in conjunction with Dr. Lipton.

[59] Dr. Allan Lipton is a professor at the Department of Medicine, in the Division of Hematology and Oncology at Pennsylvania State University. He has experience in the treatment of prostate cancer with adrenal steroid synthesis inhibitors and corticosteroids (e.g. glucocorticoid) with a focus for 40+ years on prostate cancer care and research. He was qualified as a medical doctor who is expert in the field of medical oncology and specifically in the treatment of patients with prostate cancer.

[60] Dr. Lipton, whose evidence is also considered in the context of Dr. Nam, covered the background of the disease and the treatment. He opined that by 2006, it was well known that CYP17 inhibitors (such as ketoconazole and aminoglutethimide) were useful in the treatment of prostate cancer because they impaired the production of adrenal steroids and thus prevented the conversion to testosterone. However, they also impaired the production of cortisol, resulting in the overproduction of ACTH, and the rise in mineralocorticoids with life threatening effects. It was known that glucocorticoids could address these issues; reduce mineralocorticoids, deal with adrenal insufficiency and hypertension.

[61] He spoke to the knowledge of a POS and that as of 2006, the prior art provided three independent motivations to combine AA with PN for prostate cancer – 1) PN would provide glucocorticoid replacement to address known AA side effects; 2) PN would provide palliative relief and improve quality of life; and 3) both PN and AA were known as active anti-cancer

agents with different methods of action in treating prostate cancer. The Court puts considerable weight on this conclusion as it summarizes the weight of the evidence on this issue of motivation.

[62] Dr. Lipton canvassed the relevant literature and addressed the expectation that AA could treat prostate cancer, as a known CYP17 inhibitor since 1994. Likewise, he concluded that by 2006 (or even earlier) a POS would have known that PN alone could be used as an active anti-cancer agent. He traced the reasons why it would have been obvious to try to create the combination as found in the Patent.

[63] The Court found Dr. Lipton's evidence, while not without some blemishes, to be thorough, knowledgeable and balanced. The Court places considerable reliance on that evidence.

[64] Dr. John Bantle is a medical endocrinologist, has held numerous positions in the Department of Medicine at the University of Minnesota Medical School and is now a Professor Emeritus. He was qualified simply as an expert in the field of endocrinology. He has extensive knowledge and experience in the field since 1972.

[65] He outlined the background knowledge of AA particularly that by inhibiting CYP17 (crucial to the adrenal and glucocorticoid pathways), AA substantially inhibits the glucocorticoid and androgen pathways and thus the cholesterol molecules instead follow the mineralocorticoid pathway (see Schedule A) resulting in much higher, possibly excessive, mineralocorticoid levels. A resulting drop in adrenal androgens can be life threatening. Both disorders of

mineralocorticoid excess and adrenal insufficiency are associated with a host of serious side effects. The Synacthen test – rejected as a useful tool in this case by Dr. Auchus – was used to determine cortisol response and thus adrenal insufficiency.

[66] There was a sharp debate between Dr. Bantle, who believed that AA could lead to adrenal insufficiency by blocking cortisol production, and Dr. Auchus who believes that corticosterone which is not blocked can compensate for the lost cortisol. It is not for the Court to settle the scientific debate but to note that Dr. Bantle reflected the CGK at the time and what a POS would understand.

[67] Dr. Bantle opined that due to the similarity between ketoconazole and AA, a skilled endocrinologist would have been motivated to administer AA with concomitant glucocorticoid therapy. He also addressed some of the literature and concluded that O'Donnell, in addressing the need for further studies of AA, was directed more at when a glucocorticoid (such as PN) would be administered with AA rather than if a glucocorticoid was required "if at all".

[68] Dr. Bantle's report was thorough and balanced. He responded properly to questions and was unflappable. He exhibited the teacher's desire to educate rather than to advocate. His evidence is, where necessary, favoured over his opposite number Dr. Auchus, discussed earlier.

[69] Dr. Ian McKeague is a professor of biostatistics at Columbia University. He was qualified as an expert in statistics, including biostatistics, clinical trial design, and statistical analysis of clinical trial results.

[70] Dr. McKeague was the counter expert to Dr. Ballman. He spoke to statistical principles, the AA clinical trials, the comparison of median TTTP and concluded that in looking at the publications Attard 2009 and Ryan 2011, there were too many differences to allow for a cross-study comparison and then proceeded to do what he criticized Dr. Ballman for doing, by doing his own cross-study.

[71] The critical difference between Dr. McKeague and Dr. Ballman is that Dr. Ballman had the subject matter (oncology) knowledge and experience to exercise her professional judgment. She could reach conclusions based on her knowledge and experience which Dr. McKeague was not prepared to and could not do. As indicated earlier, the Court is prepared to accept this exercise of judgment even with many of the frailties to which Dr. McKeague referred.

[72] Ms. Susanne Picard is a pharmacist and owner of SPharma Inc, a regulatory consulting firm covering a range of health products. She was qualified as a pharmacist and regulatory affairs consultant who is expert in the approval of pharmaceutical products and their labelling (including Product Monographs) by Health Canada, the regulations, guidances and protocols governing same.

[73] Ms. Picard's evidence focused on the requirements for product monographs and the Defendants' Product Monographs. She confirmed that based on her knowledge of the draft Product Monographs, none of the Defendants could be permitted to market their AA product (and in the case of Apotex, its PN product) as having an anti-cancer effect. There were inconsequential differences between the Defendants' referenced Products.

IV. Common General Knowledge/State of the Art

[74] CGK is the information generally known at the relevant time by the person skilled in the field of art or science to which the patent relates. It does not include all the information in the public domain (*Apotex Inc v Sanofi-Synthelabo Canada Inc*, 2008 SCC 61 at para 37 [*Sanofi*]).

[75] The state of the art is a wider field (*Hospira Healthcare Corporation v Kennedy Trust for Rheumatology Research*, 2020 FCA 30 [*Hospira* FCA]) but in this case the parties are not disputing the state of the art largely represented by professional articles, abstracts and the like.

[76] During the trial the Court was referred to a number of pieces of prior art by Zoom screen share. As useful as the portions were, particularly in cross-examination, the full text of each must be considered to have an appreciation of the state of the art and the CGK.

[77] The Court was referred, often tangentially, to other publications. As an aside, but in the context of the timing of this trial, references were made to Fauci papers – the Dr. Fauci of COVID-19 fame.

A. *Re Abiraterone Acetate*

[78] Barrie 1994 concluded that AA was worthy of further study as a potential agent for the treatment of hormone dependent prostate cancer.

[79] O'Donnell 2004 (a *British Journal of Cancer (2004)* paper by the lead author O'Donnell) reported on the first human trial of AA. It was an AA monotherapy trial conducted by ICR. Aside from concluding that AA was safe and that there should be further study because of the enhanced testosterone suppression, it also suggested that AA was a suitable second-line (post-castration) treatment. It also identified that ketoconazole, while an unselective inhibitor, had an anti-tumour effect (a clinical benefit evidenced by a reduction in PSA). A more selective inhibitor could be a second-line agent.

[80] A few later publications speculated that AA might be a good subject for further study in humans noting it inhibited both the hydroxylase and lyase function of the CYP17 enzyme.

[81] O'Donnell 2004 confirmed AA's role in cancer treatment by noting AA's ability to sustain testosterone suppression in castrate males, when given in 500-800 mg doses. It indicated AA could be a second-line treatment.

B. *Re Prednisone*

[82] With respect to PN, the relevant publications start with Tannock 1996 although PN was a known compound before then.

[83] Tannock 1996 was a publication study involving patients having refractory prostate cancer with pain. Patients received a chemo drug with PN or PN alone. The publication disclosed that, in combination with the chemo drug mitoxantrone, PN, dosed at 10 mg per day, would provide palliation to hormone-resistant prostate cancer patients.

[84] This was followed by Sartor 1998 which considered PN's effect on PSA levels in patients with hormone refractory prostate cancer. It showed that 34% achieved a PSA decline of at least 50% and 14% achieved a PSA decline of 75%. The result was that 48% of the patients achieved greater than 50% PSA decline. Some criticism was leveled that the results did not reach Guidelines of 50% of patients but one cannot discount that the results were pointing to PN being tolerated and having an anti-cancer effect in a subset of prostate cancer patients.

[85] In Fossa 2001, the results were less encouraging with only approximately 20% of patients having a PSA decline of greater than 50%. However, it concluded that "… monotherapy with low cost PN should be considered as first-line, standard hormonal manipulation of HRPC but the combination with tolerable cytotoxic treatment should be explored further".

[86] The following year in Fakih 2002, the authors concluded that a glucocorticoid may exert an anti-tumour effect on androgen-independent prostate cancer by suppression of adrenal androgens.

[87] Lastly, in this review of the literature related to PN, was Harris 2002 which was a prospective Phase II study. It concluded that "… glucocorticoids alone may have anti tumour effects mediated either by direct interaction with androgen receptors or by feedback inhibition of the hypothalamic-pituitary-adrenal axis".

[88] To complete the picture, the prior art taught the use of combination agents to treat prostate cancer. Gerber 1990 dealing with ketoconazole and PN in refractory prostate cancer,

noted that a small group of patients despite having had androgen ablation would benefit from ketoconazole and glucocorticoid treatment.

[89] O'Donnell 2004 referred specifically to AA and the need to determine if concomitant therapy with a glucocorticoid was required on a continuous basis at a time of psychological stress.

[90] Vidal 2004 (where Dr. de Bono was an author), in addition to addressing the use of low dose steroids as inhibiting key enzymes, noted that combining drugs could improve outcomes.

[91] The CGK addressed AA's role, PN's role and the use of the combination of compounds on the treatment of prostate cancer.

V. The Invention

[92] The inventors did not discover either of the drugs in this combination. AA was first synthesized and described in 1994. Ten (10) years later a small California company, Cougar Biotechnology, Inc was given the rights to develop AA. The first clinical trials sponsored by Cougar began in December 2005 and were led by Dr. de Bono.

[93] Before the clinical trials commenced, the state of the art known to a POS (it was generally agreed that there is no substantive difference between the state of the art and the CGK) was that despite castration, prostate cancer cells were still being stimulated by testosterone produced in the adrenal glands. Thus, hormonal therapies targeted at reducing adrenal androgens

(testosterone) could still be useful for patients with androgen independent prostate cancer. It was also known that CYP17 inhibitors (aminoglutethimide and ketoconazole) had demonstrated modest anti-tumour activity due to their ability to suppress adrenal androgen synthesis. As such, more selective CYP17 inhibitors were sought.

[94] Prior to commencing the trials it was known that AA was a CYP17 inhibitor which could treat prostate cancer. Others had determined that AA was a potent irreversible CYP17 inhibitor. De Bono's colleagues at ICR had conducted three Phase I trials administering AA to castrate and non-castrate prostate cancer patients.

[95] PN was also known to suppress the androgens that stimulate prostate cancer cell growth. For this reason, combined with the widely known palliative effects associated with them, PN and other glucocorticoids were frequently administered as the "standard of care" in advanced prostate cancer patients.

[96] Dr. de Bono knew all the above and that administering AA without a glucocorticoid could lead to endocrine toxicity. Although he knew that administering glucocorticoids including PN would protect patients from side effects, and despite pressure from his colleagues, Dr. de Bono resisted adding a concomitant glucocorticoid at the outset of the first study – COU-AA-001 [001 Study] because he wanted a "clean" study of AA unhindered by any other anti-cancer drug's impact although he knew that administering glucocorticoids including PN would protect patients from side effects.

[97] The purpose of the 001 Study in 2005 was to evaluate the safety, tolerability and efficacy of AA monotherapy in chemotherapy naïve men (men who had not been treated with chemotherapy) with mCRPC. It led to the selection of 1000 mg/day dosage of AA.

[98] The 001 Study was part of the testing of Dr. de Bono's hypothesis, described earlier. He designed an Extension Study of 001 where dexamethasone (the glucocorticoid available at ICR) would be added as the PSA score rose. This aspect was an exploratory study. His idea met with opposition from colleagues to the notion of waiting to add a glucocorticoid – not to the idea that it was necessary to administer a glucocorticoid with AA.

[99] The 001 Study showed that AA could be effective in treating prostate cancer and that after the patient stopped responding to AA monotherapy, the addition of a glucocorticoid could lead to a renewed response thereby "reserving resistance to AA".

[100] The results of the 001 Study were reported in O'Donnell 2004. It is a critical document, particularly as to "obviousness". A key passage referred to frequently is:

> In the clinical use of both aminoglutethimide and ketoconazole, it is common practice to administer supplementary hydrocortisone and this may prove necessary with 17α-hydroxylase/$C_{17,20}$–lyase inhibitors such as abiraterone acetate. However, the omission of glucocorticoid replacement when treating aminoglutethimide and ketoconazole has been shown to be safe and effective (Eichenberger and Trachtenberg, 1988; Dowsett *et al*, 1988; Harnett *et al*, 1987; Rostom *et al*, 1982). In the light of this clinical evidence, further studies with abiraterone acetate will be required to ascertain if concomitant therapy with glucocorticoid is required on a continuous basis, at times of physiological stress, if patients become symptomatic or indeed at all.

[101] Depending on perspective, O'Donnell 2004 says no more than that safety is assured and further study is required. However, others contend that O'Donnell 2004 makes clear that any future studies of CYP17 inhibitors like AA (as to when (if) to administer) require concomitant administration of a glucocorticoid.

Much was also made by the Plaintiffs as to the fact that aminoglutethimide and ketoconazole were administered – not PN.

[102] The 001 Study was the subject of comments, discussions and papers, some of which are named below. It was presented (in poster form) in June 2007 to the American Society of Clinical Oncology and written out in Attard 2008 and Attard 2009.

[103] Discovery documents of e-mails showed the nature and level of concern that glucocorticoids were not being administered early for patient safety when using AA. This evidence included the FDA in 2005 which, at that time, required glucocorticoid replacement in any multi-dose study, suggesting a glucocorticoid with minimal mineralocorticoid activity such as PN instead of hydrocortisone or dexamethasone.

[104] Despite FDA concerns, AA monotherapy testing was permitted with reported incidents of hypokalemia, hypertension and other side effects. The notion of AA monotherapy ended in March 2008 when a patient on another study suffered hypokalemia and died.

[105] The next two studies, COU-AA-002 [002 Study] and COU-AA-003 [003 Study] were designed to test the efficacy of AA monotherapy in chemotherapy naïve men and then in post-

chemotherapy men. These studies began in July and November 2006. The 002 Study was amended in May 2007 to allow a combination of AA and PN and the 003 Study permitted low dose steroids if needed.

[106] As confirmed by the Agreed Facts and various witnesses, as of August 2007, the results from several patients in the 002 and 003 Studies confirmed that AA monotherapy was safe. The studies showed that glucocorticoids can contribute to the anti-cancer effect of the combination with AA.

[107] However, regulatory approval for AA based on Phase III studies (conducted after the Canadian filing date) were based on use of AA and PN in combination.

[108] With respect to these Phase III studies, Dr. de Bono stated that the combination of AA and PN demonstrated an unexpected survival benefit in patients; however, he did not refer to an anti-cancer effect as being surprising. Dr. de Bono and many other witnesses alternated references between “survival benefits” and “anti cancer effects” whereas these are different concepts in the context of this litigation.

Despite de Bono being a named inventor, the 422 Patent does not refer to or rely specifically on his work. In fact, the invention is not the concept de Bono was working on. However, that fact does not invalidate a patent.

VI. Claim Construction

A. *Person of Ordinary Skill*

[109] The description of the person of ordinary skill [POS] is well settled in *Free World Trust v Électro Santé Inc*, 2000 SCC 66 at para 44 [*Free World Trust*] - "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". *Hospira* FCA underlines the lack of inventiveness of the POS.

[110] The parties agree to the description of the POS (slightly different from 2019 NOC) as a physician specializing in medical oncology or urology, who would have knowledge of or access to individuals having expertise in a related field including endocrinology. The 422 Patent is directed to a physician specializing in urology or medical oncology who has a significant practical experience in the treatment of patients with prostate cancer with knowledge of endocrinology and/or would have access to an endocrinologist.

B. *Claims*

[111] The parties have not argued strenuously about claim construction. The claims of the Patent must be construed from the perspective of a POS as of the publication date, February 28, 2008. There is no suggestion that there is any difference in construction between August 23, 2007 and February 28, 2008.

[112] The principles of claim construction in Canadian patent law were laid out by the Supreme Court of Canada in *Whirlpool Corp v Camco Inc*, 2000 SCC 67 at paras 49-55 and *Free World Trust* at paras 44-54. These principles are as follows:

i. Claims are to be read in an informed and purposive way, with a mind willing to understand and viewed through the eyes of the skilled reader, as of the date of publication, having regard to the common general knowledge.

ii. Adherence to the language of the claims allows them to be read in the manner in which the inventor is presumed to have intended, and in a way that is sympathetic to accomplishing the inventor's purpose, which promotes both fairness and predictability;

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

iv. On a purposive construction, the claim language will show that some elements are essential while others are non-essential. The identification of claim elements as essential or non-essential is made on the basis of the common general knowledge of the worker skilled in the art to which the patent relates as of the patent publication date.

[113] Construction is done once, for all purposes (validity and infringement), approached with a mind willing to understand. Specifications may be helpful in interpretation; they cannot expand or contract the claim.

[114] The 422 Patent deals with the treatment of prostate cancer through the use of a 17α-hydroxylase/$C_{17,20}$–lyase inhibitor such as AA in combination with at least one additional therapeutic agent such as an anti-cancer agent or a steroid. The inhibitors comprise a large number of compounds.

[115] The Patent states that AA was already known as a treatment for prostate cancer. The Defendants contend that this is an "admission binding on Janssen" (see *Bristol-Myers Squibb Canada v Apotex Inc*, 2017 FC 296 at para 183 and cases cited).

There appears to be no dispute from the Plaintiffs on this fact nor given the CGK evidence, could there be.

[116] Importantly, the Disclosure outlines that "at least one additional therapeutic agent can be a vast array of hundreds of other drugs consistently at least seventy known functional categories" including the steroids dexamethasone and PN.

[117] The Patent Office file history discloses that the claims were originally set out broadly but did not contain the exact same wording as the Asserted Claims. Those claims were re-written in 2013 to eliminate any reference to compounds other than AA and PN. The Defendants point out that this after-the-fact validation theory, at least in the context of a utility analysis, is inconsistent with patent policy.

> In my view, with respect, Glaxo/Wellcome's proposition is consistent neither with the Act (which does not postpone the requirement of utility to the vagaries of when such proof might actually be demanded) nor with patent policy (which does not encourage the stockpiling of useless or misleading patent disclosures). Were the law to be otherwise, major pharmaceutical corporations could (subject to cost considerations) patent whole stables of chemical compounds for all sorts of desirable but unrealized purposes in a shot-gun approach hoping that, as in a lottery, a certain percentage of compounds will serendipitously turn out to be useful for the purposes claimed. Such a patent system would reward deep pockets and the ingenuity of patent agents rather than the ingenuity of true inventors.
>
> *Apotex Inc v Wellcome Foundation Inc*, 2002 SCC 77 at para 80

[118] The Asserted Claims each refer to the use of a therapeutically effective amount of AA and a therapeutically effective amount of PN for the treatment of prostate cancer (Claims 3, 6 and 7), refractory prostate cancer (cancer that is not responding or insufficiently responsive to treatment or is recurring or relapsing) (Claim 14), and refractory prostate cancer that is specifically non-responsive to one or more anti-cancer agents (Claim 15) (Court underlining). The non-asserted claims are essentially the same.

[119] The definitions are obviously important to claim construction. In this case the patentee creates its own lexicon which governs the interpretation of the Patent. The important ones for this purpose:

- "therapeutically effective amount of abiraterone acetate" and "therapeutically effective amount of prednisone": an amount of AA effective for treating prostate cancer and an amount of PN effective for treating prostate cancer.
- "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.

[120] The phrases "therapeutically effective amount of abiraterone acetate …" and "therapeutically effective amount of prednisone" describe the use and quality of each to treat prostate cancer when used in combination.

[121] "Treating" (or treatment) includes "the eradication, removal, modification, management and control of a tumor, or primary, regional or metastatic cancer cell or tissue and the marginalization or delay of the spread of cancer".

The definition covers the effect on the tumour or cancer cells. It does not address other palliative effects or other side effects nor does it address, much less, require, that there be a

"survival benefit". Nor does it assert a greater anti-cancer effect, duration of effectiveness or a reversal of resistance to any drug.

[122] An "anti-cancer agent" is any therapeutic agent that directly or indirectly kills, prohibits, stops or reduces the proliferation of cancer cells. Contrary to the Plaintiffs' argument, the definition does not say that the actions of an anti-cancer agent necessarily occur when used only in combination with AA – that is Dr. Rettig's interpretation, not the Court's.

[123] Lastly, in my view, as held in 2019 NOC, each of AA and PN must be effective to treat prostate cancer. While the Plaintiffs contend that there is no practical reason why each agent would have to be effective when given alone, that is what the claims say.

Further, and unlike in 2019 NOC, there is sufficient evidence that PN was known to have some anti-cancer effect along with its long recognized palliative effects.

[124] Having completed the Claim Construction analysis, it is more useful to first deal with the validity issues, particularly obviousness, as it is dispositive of this litigation. The Court also addresses the allegation of infringement so that the parties, at least, have a complete resolution of the points in this litigation.

VII. Validity

A. *Obviousness/Obvious to Try*

(1) Framework

[125] Section 28.3 of the *Patent Act*, RSC 1985, c P-1, requires that "the subject matter defined by a claim" must not have been obvious on the claim date to a skilled person having regard to the state of the art.

In the present case, the Defendants claim that this is a case of "obvious to try" – a variation on the theme of obviousness.

[126] Justice St-Louis in *Eli Lilly Canada Inc v Mylan Pharmaceuticals ULC*, 2020 FC 816, provided a helpful review of the confusion in the law over recent years as to "obviousness, claims and inventive concepts". The Court takes its immediate guidance from *Hospira* FCA, and focuses its inquiry on the Asserted Claims in the 422 Patent. A critical question is, having regard to the Asserted Claims, what was inventive (not obvious) about combining AA and PN (in the specific amounts) to treat prostate cancer including refractory prostate cancer.

[127] The Plaintiffs assert that it would not have been self-evident to a POS to combine AA with PN wherein both agents contribute to the efficacy of the combination, in part because the mechanism for resistance to hormonal therapy in mCRPC was not understood. The Plaintiffs argue that it would not have been self-evident to add a glucocorticoid in the hopes of generating a renewed response to AA after being clinically resistant to AA.

As discussed under Claim Construction, the Asserted Claims do not address or claim reversal of resistance to AA.

[128] The state of the art is not confined to that art which would have been disclosed by a reasonably diligent search - except potentially at Step 4 of the *Sanofi* obviousness analysis (*Hospira* FCA at para 86). In any event, the choice of the state of the art is in the hands of the party alleging obviousness.

[129] The obvious analysis in *Sanofi* lays out four steps:

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

[130] The notional POS has certain qualities of a competent technician (deduction and dexterity) but lacks others (inventiveness and imagination). The quality of inventiveness

concerns ability to look at a problem in a way that would not be obvious to others in their field (*Hospira* FCA at para 80).

[131] In *Sanofi*, the Supreme Court laid out the current analytical framework "where advances are often won by experimentation", an "obvious to try" test might be appropriate.

[132] At para 66 of that decision, the Supreme Court set out the benchmark to be met:

> For a finding that an invention was "obvious to try", there must be evidence to convince a judge on a balance of probabilities that it was more or less self-evident to try to obtain the invention. Mere possibility that something might turn up is not enough.

[133] The Supreme Court in *Sanofi* also provided the following guidance as to what are effectively four factors to be considered an obvious to try circumstance:

> [69] If an "obvious to try" test is warranted, the following factors should be taken into consideration at the fourth step of the obviousness inquiry. As with anticipation, this list is not exhaustive. The factors will apply in accordance with the evidence in each case.
>
> 1. Is it more or less self-evident that what is being tried ought to work? Are there a finite number of identified predictable solutions known to persons skilled in the art?
>
> 2. What is the extent, nature and amount of effort required to achieve the invention? Are routine trials carried out or is the experimentation prolonged and arduous, such that the trials would not be considered routine?
>
> 3. Is there a motive provided in the prior art to find the solution the patent addresses?
>
> [70] Another important factor may arise from considering the actual course of conduct which culminated in the making of the invention. It is true that obviousness is largely concerned with how a skilled worker would have acted in the light of the prior art. But

> this is no reason to exclude evidence of the history of the invention, particularly where the knowledge of those involved in finding the invention is no lower than what would be expected of the skilled person.

[134] It should be noted that, whereas being "more or less self-evident to try to obtain the invention" (*Sanofi* at para 66) is a requirement for obviousness to try, being "more or less self-evident that what is being tried ought to work" (*Sanofi* at para 69) is not a requirement but a factor to be considered.

[135] As to "ought to work", it is clear that certainty of success is not required otherwise there would be no point in describing it as something "to try". "Trying" implies the possibility of failure but with the expectation of success. While never easy to define on a spectrum of likely success, it is neither a Boston College Doug Flutie "Hail Mary" pass nor a Wayne Gretsky "open net shot". Some limited experimentation is permitted in the context of the second factor. It is not to be arduous, inventive or unusual.

[136] The assessment of the factors listed in the above paragraph is a fact driven exercise, dependent on the specific facts of the case. The 4th factor is closely tied to the 2nd (*Sanofi*, para 71).

[137] The Court is required to assess and weigh the factors, some having more weight than others in a given case, in reaching its conclusion as to "obvious to try". The Court must avoid the benefit of hindsight. Virtually everything is obvious once it is discovered.

(2) Step 1 – State of the Art/Common General Knowledge – August 23, 2007

[138] The starting point of the obvious to try analysis is the relevant state of the art/CGK. Except for Dr. Rettig's reliance on state of the art in relation to survival benefit, there was little disagreement on the state of the art. The Defendants' closing submissions set out the state of the art clearly and a synthesis of the evidence discussed earlier.

Dr. Rettig, in one of his many recantations of evidence under cross-examination, recognized that the treatments in the 422 Patent did not have to establish a survival benefit and ultimately agreed with many of the points made by the Defendants' experts (see, as examples, Transcript – pp 1545-1558).

[139] As Dr. Lipton established, when cancer cells become CRPC, a second-line hormonal therapy reducing testosterone produced in the adrenal glands can be used.

The art taught that prostate cancer responded to hormone therapy.

[140] A key indicator in the treatment of prostate cancer (as that term treatment is used in the Patent and the art) is the PSA score (prostate-specific antigen) – a common test given to men in mid to later life. According to the NCCN 2007 guidelines and used in the profession, a "PSA response" is considered to be a decline of at least 50% confirmed by a latter test four or more weeks later, which indicated that patients were likely to have experienced a clinically significant response – an anti-cancer effect.

The PSA score was a surrogate for treatment in prostate cancer and a key marker of progression (a negative) or decline in cancer cells (a positive).

[141] Aminoglutethimide, ketoconazole and AA were known CYP17 androgen inhibitors, part of a class of drugs used for treating mCRPC. They inhibit enzymes that produce testosterone from cholesterol. This was confirmed by Drs. Nam and Lipton and while denied by Dr. Rettig in the 2019 NOC, it is apparently accepted by him now.

[142] As established by Drs. Nam and Lipton, aminoglutethimide was known to have anti-cancer treatment effects in prostate cancer patents. A fact which Dr. Rettig, having denied it in the 2019 NOC, was forced to concede.

[143] Ample evidence from experts and from studies establish that ketoconazole was known to have anti-cancer treatment effects. Again, Dr. Rettig had to concede this point having denied it in the 2019 NOC. He admitted to using ketoconazole with PN for prostate cancer.

Ketoconazole was used off label for the treatment of prostate cancer because it reduced testosterone. It was also recommended for use in the 2005 and 2007 NCCN Guidelines.

[144] Importantly, administering adrenal androgen inhibitors were known to affect multiple steroid production pathways and compromise cortisol production. Aminoglutethimide and ketoconazole were used as glucocorticoid replacement.

There were several ways of managing adrenal insufficiency, low adrenal reserve and mineralocorticoid excess. However, glucocorticoid replacement with PN, dexamethasone or hydrocortisone was a common clinical practice. PN was known to have palliative and anti-cancer effects as discussed later.

[145] AA, a CYP17 inhibitor, had been shown to be useful in the treatment of prostate cancer. The role of CYP17 inhibitors (also referred to as androgen inhibitors) in treating prostate cancer is acknowledged in the 422 Patent.

[146] Early publications such as Gerber 1990 suggest that where PSA levels are increasing, patients can be treated with a combination of ketoconazole and a glucocorticoid. Potter 1995 and Barrie 1994 described AA activity in vitro and in animals. AA was built upon ketoconazole and O'Donnell 2004 noted that AA resulted in the suppression of testosterone below castrate levels. O'Donnell 2004 is an important paper in the art, its limitations were discussed earlier, but the weight of the evidence is that O'Donnell pointed the way to the Patent.

[147] AA was administered with a glucocorticoid replacement, as was the case with ketoconazole and aminoglutethimide. The need for a glucocorticoid replacement was recognized even by Dr. de Bono who wanted to avoid using a glucocorticoid replacement in his studies for as long as possible.

[148] The evidence establishes that AA was more selective than the other two known CYP17 inhibitors, which had the desirable effect of decreasing androgens but the undesirable effects of reduced cortisol levels and increased mineralocorticoids. The net effect was to have both adrenal insufficiency and mineralocorticoid excess – potentially fatal if left untreated.

[149] O'Donnell 2004 referred to abnormally low cortisol levels as evidenced by the Synacthen tests. The role and importance of Synacthen tests is referenced earlier in respect of Dr. Bantle's evidence.

[150] As Dr. Bantle indicated, a skilled endocrinologist would be concerned for AA inducing low adrenal reserves and adrenal insufficiency and mineralocorticoid excess. As he discussed, an endocrinologist would be consulted in respect of Synacthen tests and the adverse effect of AA. Dr. Auchus' evidence on this issue was not persuasive.

[151] The cautionary note in O'Donnell 2004 about future studies has been discussed earlier. However, the Court concludes that the weight of the evidence is that a skilled person, having regard to the experience with aminoglutethimide and ketoconazole, would expect side effects from AA and would expect that concomitant therapy with a glucocorticoid would be required.

[152] In that regard, the Court accepts Dr. Bantle's explanation that PN could effectively treat adrenal insufficiency, low adrenal reserve and mineralocorticoid excess. Adding a glucocorticoid such as PN replaces the natural cortisol that the body would normally produce but for AA including but not limited to hypertension and hypokalemia.

[153] It was recognized that all drugs can have side effects – the example of having to take an antacid when taking an over the counter arthritis drug was an effective illustration of the point. However, the side effects of glucocorticoids including PN would not have deterred a skilled

endocrinologist from administering those drugs. Dr. Auchus' solution of prescribing spironolactone – known to exacerbate prostate cancer – is unsupported.

[154] The use of AA or a CYP17 inhibitor in combination with a glucocorticoid in treating prostate cancer was clearly in the minds of skilled persons as evidenced by numerous review articles, textbooks and clinical trials underway. AA, because of its more selective quality, was clearly a target therapy.

[155] I conclude that a POS would have seen ketoconazole's results as a basis to take the next investigative step with AA by replacing ketoconazole with AA as AA was a superior more selective inhibitor. Even the dosage at 10 mg per day may be carried from the one compound to the other.

[156] PN was known to treat prostate cancers. It had three effects – 1) an anti-cancer effect (as per the 422 Patent definition); 2) as a glucocorticoid therapy replacement; and 3) for palliation for which it was best known.

The evidence of Drs. Nam and Lipton confirm the above and various publications such as Tannock 1989, Sartor 1998, Fossa 2001, Fakih 2002 and Lam 2006 speak to that issue and confirm the path to discovery.

[157] There was no serious concern that glucocorticoids and PN in particular would cancel out or interfere with the anti-cancer activity of CPY17 inhibitors like AA.

[158] The use of anti-cancer agents in combination was well accepted. In respect of the anti-cancer activity of PN (and other glucocorticoids), they had been recognized when used with aminoglutethimide and ketoconazole. Dr. de Bono acknowledged this fact but used another glucocorticoid initially because it was the one readily available at IRC.

[159] PN was best known and used for its palliative effects providing relief from the effects of cancer and improving the quality of life, particularly for those patients with end state prostate cancers.

[160] In summary, the prior art for AA disclosed that the suppression of serum testosterone and adrenogenic precursor levels were predicted. AA was being studied and review articles advised that any patient receiving AA ought to be closely monitored for signs of adrenal insufficiency, mineralocorticoid excess and other side effects discussed above. The need for concomitant glucocorticoid treatment was also recognised.

[161] Unlike in 2019 NOC where the evidence took one *close* to the point of co-administration of AA with PN to provide anti-cancer effects, the evidence in this case demonstrates that it was obvious to do so. The evidence to the contrary has been shown to be seriously flawed.

[162] As stated earlier, the issue is not absolute proof of the science but the accepted CGK of the POS and the state of the art. A POS would have seen such co-administration as a logical step – obvious to try.

(3) Step 2 – The Differences between the State of the Art and the Asserted Claims

[163] The Plaintiffs argue that the differences between the invention of the 422 Patent and the CGK/State of Art as of August 2007 were too significant (for ease of reading, the particulars are in quotes).

[164] "AA was not known to treat prostate cancer." This is not the case. As shown in O'Donnell 2004, AA had the ability to sustain testosterone suppression in castrate males at 500-800 mg daily dose, suggestive of its use as a second-line hormonal therapy.

[165] In my view, the evidence is that AA had been identified in the prior art as an effective second-line prostate cancer treatment. It was better than ketoconazole because it was more selective and therefore would suppress testosterone production in a more targeted way, without also inhibiting the production of other important steroid hormones like aldosterone.

[166] The dosing ranges for AA and PN were even taught in the prior art (at 800 mg/day and 10-20 mg/day, respectively, although O'Donnell 2004 was concerned that 800 mg was not sufficient).

[167] One must conclude that the prior art did not teach away from this combination but towards it.

[168] "PN was not known to effectively treat prostate cancer." The evidence particularly from Drs. Nam and Gotto is that it was known to treat prostate cancer – how and how well were not known but given the Patent's absence of performance thresholds, the latter point is not relevant to the Asserted Claims.

[169] "The art did not teach that AA and PN should be combined." As discussed above, AA treatment was known to be used with a glucocorticoid to prevent adrenal insufficiency, and PN was a logical choice of glucocorticoid.

(4) Step 3 – Differences between the State of the Art and the inventive concept of the claim or the claim as construed

[170] While there were some differences between the CGK and the Asserted Claims, they are not so material that a POS would not continue down the road to the invention. To a POS the CGK and state of the art suggests that AA could be combined with PN with a reasonable probability of success in treating the cancer.

[171] The inventive concept of the Asserted Claims are the use of the combination of therapeutically effective amounts of AA and PN in the treatment of prostate cancer (Claims 3, 6 and 7), refractory cancer (Claim 14) and refractory prostate cancer that is not responding to an anti-cancer agent (Claim 15) in a human. This is the same as the claims construed.

[172] In response to the Plaintiffs' claim of alleged differences (Plaintiffs' Closing Written Submissions, para 77), the Court has found:

a) AA was known to effectively treat prostate cancer.

b) PN was known to effectively treat prostate cancer.

c) The state of the art did teach combination of drugs like AA and PN.

As outlined in subsequent paragraphs, arriving at the Asserted Claims would not have required ingenuity.

[173] The only part of the puzzle missing in the state of the art/CGK is a person actually combining AA and PN to treat prostate cancer including refractory prostate cancer. Given the evidence, to do so was a logical step in the progress of prostate cancer treatment.

[174] It was logical to combine a CYP17 inhibitor with a glucocorticoid and more particularly AA with PN to treat prostate cancer including non-responding refractory prostate cancer. Drs. Nam and Lipton confirm it; even Dr. Rettig had done it with ketoconazole and hydrocortisone or PN.

There were ample reasons for a POS to combine AA and PN in the treatment of CRPC.

[175] The Plaintiffs continually rely on the absence of a survival benefit in any drug treatment other than docetaxel to suggest that it was not at least obvious to try AA and PN. While looking for a survival benefit may have affected some researchers' reasons to try, it was sufficiently logical to combine AA and a readily available glucocorticoid for Dr. de Bono to do.

[176] PN was known from the 1980-1990s to have anti-cancer effects and despite the age of that knowledge, there is no evidence that the CGK disavowed that knowledge of modest and short-lived PSA declines. This was well set out in various publications.

[177] In Tannock 1996 the authors concluded that mitoxantrone plus PN provides better palliation than PN alone. Tannock 2004 compared docetaxel plus PN to mitoxantrone plus PN and found that the former offered higher overall survival benefit, better pain control, improved quality of life and more frequent PSA responses than the latter. Tannock 2004 referred to low dose PN or hydrocortisone as being palliative, and it was seen by Dr. Nam as encouraging to a POS.

[178] Sartor 1998 further suggests that PN can reduce PSA levels – a marker of anti-cancer effect. The use of PN in that publication was for monotherapy in mCRPC patients. Importantly, Sartor 1998 disclosed that PN had anti-cancer effects. Fossa 2001, Fakih 2002 and Harris 2002 each supported Sartor 1998's conclusion.

[179] If the search for survival benefits was as important as suggested, the positive anti-cancer effects of each drug outlined above in conjunction with O'Donnell 2004 provided good reason for a POS to combine AA and PN. The inventors do not have to be seeking the same solution as the eventual patent discloses (*Hospira* FCA, para 94).

[180] These steps lead to the question of whether it would be obvious to try – to take the next step to combine AA and PN as claimed.

(5) Step 4 – Obvious/Degree of Invention

[181] In *Sanofi*, the Supreme Court of Canada clearly contemplated the very type of issue in respect of drug treatments.

> [68] In areas of endeavour where advances are often won by experimentation, an "obvious to try" test might be appropriate. In such areas, there may be numerous interrelated variables with which to experiment. For example, some inventions in the pharmaceutical industry might warrant an "obvious to try" test since there may be many chemically similar structures that can elicit different biological responses and offer the potential for significant therapeutic advances.

[182] As part of the obvious to try considerations, the Court is to take into consideration four factors – a non-exhaustive list – depending on the evidence in each case.

1. Is it more or less self-evident that what is being tried ought to work? Are there a finite number of identified predictable solutions known to persons skilled in the art?
2. What is the extent, nature and amount of effort required to achieve the invention? Are routine trials carried out or is the experimentation prolonged and arduous, such that the trials would not be considered routine?
3. Is there a motive provided in the prior art to find the solution the patent addresses? Another important factor may arise from considering the actual course of conduct which culminated in the making of the invention.
4. What was the actual course of conduct which led to the invention?

[183] On the issue of any ingenuity required, I accept the opinions of Drs. Nam and Lipton that none is required.

(6) "Self-Evident" Work

[184] Given the success of other combinations, it was reasonable to expect success in anti-cancer treatment to combine AA and PN to treat CRPC patients excluding those being refractory patients.

[185] A POS would want to combine AA and PN to obtain their combined anti-cancer effect. Each agent had been known to have this effect, similar drugs (aminoglutethimide and ketoconazole) had been used and AA was more potent and selective than ketoconazole. It was self-evident that AA and PN should work together without fear that their mechanisms of action would somehow cancel or diminish each agent.

[186] Increasing dosages from 200 to 250 mg or from 800 mg to 1000 mg was not shown to be inventive but simply logical progression. The baseline amounts had previously been established.

[187] A POS would combine AA with PN to mitigate the side effects of AA. Based on what was known about AA, the need for a glucocorticoid was expected – replacement therapy was standard conduct. This is what happened with Cougar's development of AA. There was no reason to expect that the combination would not work.

[188] Because PN was also known to have palliative effects, it was reasonable to combine it with AA for this feature as well.

[189] There was every reason to expect the combination to work. As of August 2007, a POS would not be looking at the vast array of compounds listed in the Patent's disclosure as the search had narrowed to AA and a limited number of glucocorticoids including PN.

(7) Effort Required

[190] The effort to obtain FDA approval is not the determinative issue. The parties have agreed that regulatory approval is not the requirement for the Patent. Even if it were, while clinical trials are expensive and time consuming, they are an established process, a common feature of drug companies and their operation. The evidence does not suggest that such trials were arduous or experimental or out of the ordinary.

[191] Researchers followed the line of progression in respect of the course of actual conduct with ketoconazole and aminoglutethimide in combination with a glucocorticoid.

There was no reason not to expect that the AA/PN combination would work. It would be a concern to courts if the normal work of a clinical trial was held out to be the effort that would bar an "obvious to try" analysis. It would mean that no pharmaceutical treatment which would otherwise be obvious to try would ever meet the Supreme Court of Canada's fourth step because regulatory approval would trump patent law.

[192] For purpose of treatment, the PSA score is the benchmark, not regulatory approval. The effort to establish that the combination provided an anti-cancer effect (the Patent's definition of treatment) is established by the relatively routine PSA test.

[193] Effort is but one factor to consider and any difficulty a POS may have is offset by the other factors to be considered including motive. No inventiveness was required.

(8) Motive

[194] The reasons or motive to find the solution to the Patent have been addressed to some extent under the Self-Evident Work factor. There was a general motive to find a better treatment for men suffering from a major life threatening cancer. The options available were limited in respect of prostate cancer and those suffering CRPC.

[195] The motive factor speaks also to the specific motive to create this treatment with those agents. As discussed throughout these Reasons, AA was seen as an improvement in the 17α-hydroxylase/$C_{17,20}$–lyase inhibitor agents. A glucocorticoid was required to deal with adverse effects. Patients also sought relief from side effects and pain/discomfort – all areas for which PN was known. The side effects were serious and could render the inhibitor worthless from a medical or practical perspective. The fact that PN also had an anti-cancer effect was an extra advantage over other options.

[196] A POS would be motivated to take these two agents in combination to see if they provided further benefits to the patient – in the expectation that they would.

[197] Weighing these factors together, they point to the conclusion that the combination was obvious to try.

[198] For these reasons, the Patent is obvious and therefore invalid.

[199] For reasons earlier given, the Court will address the remaining validity issues and the separate infringement issue.

B. *Utility*

[200] The utility of the invention must be demonstrated as of the filing date – August 23, 2007. The invention must "be useful, in the sense that it carries out some useful known objective". As held by the Supreme Court in *AstraZeneca Canada Inc v Apotex Inc*, 2017 SCC 36 at para 56 (relied on by both parties), the utility requirement is to prevent patenting of "a laboratory curiosity whose only possible claim to utility is as a starting material for further research". That might describe the Patent as originally filed but with the amendments to limit the claims to those now in issue, that concern is eliminated.

[201] A mere "scintilla" of utility will be sufficient – a single use related to the nature of the subject matter is sufficient. There is no issue that the invention is useful in fact.

[202] I agree with the Plaintiffs that the subject matter of the Asserted Claims is the use of AA in combination with PN for the treatment of prostate cancer (Claims 3, 6 and 7), refractory prostate cancer (Claim 14) or refractory prostate cancer not responding to at least one anti-cancer

agent (Claim 15). Utility was demonstrated by the data generated prior to August 24, 2007, including in the 001 to 004 clinical studies.

[203] The Defendants' difficulty is that much of the evidence on which it relies for Obvious to Try supports the utility of the Patent. While "sound prediction" is not specifically relied upon, Janssen does say that Dr. de Bono's work with AA and dexamethasone demonstrated the scintilla of utility.

[204] The essence of the Defendants' position, as understood by the Court, is that the Plaintiffs never demonstrated that AA and PN together actually has an anti-cancer effect ("treat the cancer"). They argue that the Plaintiffs only make out utility of dexamethasone and PN were interchangeable.

[205] The evidence establishes that PN and dexamethasone are not identical but they are sufficiently equivalent in many respects – sufficient for Dr. de Bono to believe that any glucocorticoid could suppress ACTH. As discussed earlier, a POS would appreciate the similarities relevant for the purposes of the invention.

[206] Some of the expert evidence is not helpful. Dr. Rettig seemed to think that the legal standard was a "scintilla of evidence". Dr. Nam seemed to set a high standard in dismissing data that shows that 50% of patients experienced a renewed PSA response to AA when a glucocorticoid was added. In the 2019 NOC, he had set a standard of scientific certainty but this litigation is a new case and has much better evidence on utility than in 2019. The Plaintiffs'

criticism of Dr. Nam's evidence on this issue (Plaintiffs' Closing Written Submissions, paras 117 to 124) are warranted.

[207] The standard for establishing utility is low and does not require three arm studies or a significant number of patients' results to establish the scintilla.

[208] Dr. Ballman's evidence, which the Court found helpful, points out that the data available before August 2007 showed that PN has an anti-cancer effect and contributes to the efficacy of the combination. Dr. Nam's evidence on utility has not been as consistent or helpful as has his evidence in other areas.

[209] As of August 23, 2007, a total of 15 patients experienced clinically meaningful PSA responses following the administration of AA and a glucocorticoid including PN – six of whom were from the 004 study and received the combination of AA and PN from the study outset. Several of the patients met the benchmark of a 50% PSA decline, confirmed by a second PSA value at least 28 days later. For purposes of utility, it is not necessary to meet Guidelines or FDA approvals. Utility is met if some patients, even if only those in dire circumstances, respond.

[210] Sufficient utility has been otherwise established to sustain the Patent if it was not obvious to try.

C. *Sufficiency*

[211] The Defendants contend that specification is not sufficient to teach how to work the Patent. They contend that the term "therapeutically effective amount" is not sufficiently precise as to the amount of the agent to be used. They say research is required and that is not permitted under *Teva Canada Ltd v Pfizer Canada Inc,* 2012 SCC 60.

To some extent the Defendants' position overlaps with its position on "patentable matter" discussed later.

[212] In *Consolboard Inc v MacMillan Bloedel (Sask)* Ltd, [1981] 1 SCR 504 at 525-527, the Court concluded that a patent did not have to specify how the invention works so long as it explains how to work the invention.

[213] In that regard, the Patent teaches how to treat prostate cancer by administering the combination of the therapeutic amounts. The dosages of 10-250 mg per day of PN are disclosed. Further 1000 mg/day dose of AA is disclosed (Claim 6) as is 10 mg of PN. This amount will treat prostate cancer.

[214] No persuasive evidence has been presented of a POS (who has the CGK as described) being unable to work the Patent.

[215] As with many of the following validity submissions, there is a paucity of evidence to support the Defendants' submission. The Patent and its foreign equivalents in the USA and

Europe have been in use for a number of years. Despite this use, there has been an absence of direct, practical evidence (rather than opinion evidence) from the real users/prescribers attesting to problems with understanding or using the treatment. Given the burden on the Defendants to make the case under the various headings of validity challenges, this evidentiary gap is meaningful. The contention of insufficiency is not made out.

D. *Patentable Subject Matter*

[216] The arguments of both parties on this issue of unpatentable subject matters are confusing and difficult to consider. They include the argument that the Plaintiffs are claiming a mere aggregation and a mere discovery and further that the Patent is for a method of medical treatment.

[217] The Defendants urge the Court not to follow its 2019 NOC decision on this issue citing errors and new evidence. As indicated earlier, the Court approaches this case afresh and that except where specifically mentioned, the 2019 NOC is not relevant. The Court must decide on the basis of the evidence in this trial which is significantly different on key points.

The Plaintiffs, on the other hand, do not assist the Court in that they make minimal submissions. They ask that this Court note that they are preserving their rights on the issues of aggregation and mere discovery for the pending appeal of the 2019 NOC decision.

[218] The Plaintiffs' position on these points is dependent on the invention being something new or novel. Therefore, on the basis of this decision, that position is moot.

[219] In the present case, it has been established that AA and PN each have anti-cancer effects. The Defendants argue that the combination merely adds two known substances such that the end result is mere aggregation – not something novel or synergistic.

[220] If PN had not been known to have anti-cancer effects but was only known for palliation, then the combination would have disclosed something new – an improvement over mere aggregation.

[221] In accordance with the facts as found by the Court in this litigation, the issue is academic. The Patent added nothing new as it was obvious/obvious to try.

[222] As to the matter of method of medical treatment, the Defendants say it arises from a dosage range set at .01 mg/day to 500 mg/day for PN. The selection of the precise amount within the range requires medical judgment and therefore the claims are invalid. The dosage ranges do not appear in the Asserted Claims.

[223] The issue of method of medical treatment is not a settled one and therefore a court should be cautious in striking down claims on this basis. In the present case, the ranges are not stipulated in the Asserted Claims which provide instructions on how to use AA and PN to achieve the optimal desired outcome. Again, there is no direct evidence from prescribers (practising urologists/oncologists rather than expert opinion) which speaks to being unable to know how to use the Asserted Claims.

Therefore, the Asserted Claims will not be struck on this ground alone.

E. *Listing*

[224] The issue raised but not strenuously argued is whether the eligibility challenge to the Patent being listed on the Patent Register in respect of ZYTIGA must be brought by motion or can be the subject of a decision on the merits in a section 6 action. The issue is one of procedure not whether the 422 Patent should be listed.

[225] Following on Justice Hughes' decision in *Bayer Inc v Apotex Inc*, 2014 FC 436, the listing issue can be by motion in advance of the trial or in the trial itself.

[226] As these types of cases are case managed, it would be for the case management judge to address this procedural aspect.

[227] In the current circumstances, it would be an abuse to now say that the listing issue should have been by motion and cannot be raised here, if there were merit to the proposition that the Patent should not have been listed.

[228] However, the claimed subject matter of the 422 Patent is covered by the ZYTIGA indication, as discussed in the following consideration of Infringement. It was therefore properly listed.

F. *Non Asserted Claims/Counterclaim*

[229] The Plaintiffs object to the Defendants bringing a counterclaim in respect to the non-asserted claims on the basis that the right to bring a counterclaim is restricted under s 6(3) to counterclaims in respect of "asserted claims".

[230] In the context of the present case, this counterclaim issue appears to have no particular relevance except for appellate comment.

[231] The Plaintiffs argue that s 6.01 limits an action under s 6(1) to asserted claims although those terms are not used. It says that a counterclaim under s 6(3) is specifically limited to asserted claims.

[232] There are two matters of concern to the Court. The first is that the Plaintiffs consented to the delivery of a counterclaim without reservations at the time. The second is that a defendant may not be able to claim invalidity of a patent on grounds but only as it relates to specific claims asserted in an NOC action.

[233] The NOC Regulations are not a complete code but the purpose of s 6(3) must be to confirm that the right to bring a counterclaim in the NOC action exists; but it is restricted to the claims asserted in the action.

[234] A counterclaim is a separate action. Section 6(3) merely allows a party the convenience of bringing a challenge to a patent in the context of an NOC action in respect of asserted claims. Whether a separate claim of invalidity could be consolidated with a NOC action remains an open question.

[235] Given the consent of the Plaintiffs in this case, the parties found a more expeditious way to deal with non-asserted claims, none of which impact the Judgment in this case.

[236] A more thorough analysis of the overall impact of s 6(3) of the NOC Regulations should await a better record and more fulsome legal argument.

[237] Having dealt with the validity issues, for completeness, the Court turns to the matter of Infringement.

VIII. Infringement

[238] The remaining issue is whether the Defendants will induce infringement of the 422 Patent by the third parties' users of their AA product for which they seek an NOC. In this, the Plaintiffs bear the burden (*Monsanto Canada Inc v Schmeiser*, 2004 SCC 34).

[239] To determine whether a patent claim is infringed, having purposively construed the claims and identified essential claim elements (all elements of each claim are essential), the Court must determine whether the allegedly infringing product falls within the scope of the claims (*Free World Trust* at paras 48-49). There is no infringement if an essential element is

different or omitted, but there may still be infringement if a non-essential element is substituted or omitted (*Free World Trust* at para 31).

[240] It is well established that allegations of non-infringement under the NOC Regulations refer only to actions of the "second person" – in this case the Defendants – and infringement in this context means both direct infringement and indirect infringement by inducement (*Pharmascience Inc v Sanofi-Aventis Canada Inc*, 2006 FCA 229 at paras 55-59). Absent influence by a defendant, infringement acts of third parties do not ground a finding of infringement under the NOC Regulations (*Novopharm Limited v Sanofi-Aventis Canada Inc*, 2007 FCA 167 at paras 10-11).

[241] The test for inducement is laid out in *Corlac Inc v Weatherford Canada Inc*, 2011 FCA 228 at para 162:

1. The act of infringement will be completed by the direct infringer.
2. Acts of infringement were influenced by the Defendants to the extent that without their influence, the act of infringement would not have occurred.
3. The Defendants exercised that influence knowing that it would result in the infringement.

[242] It has been described as a high bar. The bar is met if as held in *Janssen Inc v Teva Canada Ltd*, 2020 FC 593 at para 266, "… where the patent claims the use of a combination, the product monograph must direct the infringer to use the combination in order to establish inducement". The whole of the Product Monograph must be considered.

[243] The Defendants accept that there will be direct infringement "as this is presumed (one 'cannot tell a drug how to act in the body')" (Defendants' Closing Submissions, para 123 and cases cited). Also there are no issues which rest on the differences between the respective Defendants' Product Monographs. The product monographs at issue are the AA Product Monographs – not the PN Product Monograph.

[244] The Defendants' submission that the Plaintiffs have failed to prove that PN will have an anti-cancer effect when co-administered with AA for the treatment of prostate cancer, is in error. As detailed in the Validity section, PN was known for many years in advance of the 422 Patent to have this effect and Dr. Ballman's evidence, as well as other evidence heard, supports that conclusion in this case.

[245] The Defendants' Product Monographs instruct physicians to prescribe and pharmacists to dispense. AA (1000 mg/day) and PN (10 mg/day for mCRPC and 5 mg/day for newly diagnosed, high-risk hormone sensitive prostate cancer [HSPC]), together, for the treatment of prostate cancer. mCRPC is the prostate cancer covered in Claims 3, 6 and 7, refractory prostate cancer is covered by Claim 14, and refractory prostate cancer that is not responding to an anti-cancer treatment by Claim 15.

The HSPC indication, a type of prostate cancer, is specific to PMS and Dr. Reddy's Products.

[246] The above uses infringe the Asserted Claims. For example, the Apotex "Indications and Clinical Use" sections of its Product Monograph reads:

> APO-ABIRATERONE FILM COATED TABLETS (abiraterone acetate) is indicated in combination with prednisone for the treatment of metastatic prostate cancer (castration-resistant prostate cancer, mCRPC) in patients who:
>
> - are symptomatic or mildly symptomatic after failure of androgen deprivation therapy.
> - have received prior chemotherapy containing docetaxel after failure of androgen deprivation therapy.

[247] The Indications and Clinical Use section makes clear that AA and PN are to be used in combination for the treatment of mCRPC. This is a case of the Defendants indicating the use of the same agents, in the same way, for the same purpose, in the same patients by the same users.

[248] It is also clear that the use – the treatment – is not for the control of side effects. As raised in Claim Construction, "treatment" under the definitions in the Patent, in the context of management (and the other activities of eradication, etc.) relate to the "tumour or primary or regional or metastatic cancer cells or tissue and the minimization or delay of the spread of the disease". The focus is on direct effects on the cancer – not on side effects.

[249] As the experts indicated, where a drug is used solely to control side effects of a therapy, it is not included in the Indications section (see Costaris and Picard evidence).

[250] In their draft Product Monographs the Defendants cite a number of References (publications such as de Bono 2011, the Attard Reports) which address PN contributing to anti-

cancer effects of the combination with AA. PN's role in mitigating side effects is also contained in the References. It is no answer to say that although the Defendants put the References in the Product Monograph, they do not expect the doctors or pharmacists to consider them.

[251] The Defendants point to a number of places in the Product Monographs that refer to PN's role in mitigating side effects. In fact, the Plaintiffs do the same with respect to ZYTIGA.

[252] The Defendants cannot avoid liability by wishing that, in the case of using their Product, PN would not behave as an anti-cancer function.

[253] The natural consequences of the use of the Defendants' Products is the anti-cancer effect of PN in combination with AA. This is a use which the Defendants know or ought to know, which they encourage through the use of their Products. The difficulty for the Defendants is that they chose to use PN as their glucocorticoid to go with AA and that PN's properties include an anti-cancer function. It cannot control or turn off the properties of the drug but they chose the drug PN and are responsible for the natural consequences of its use. Even the Indications sections of the competing Product Monographs are the same.

[254] PN contributes to the anti-cancer effect of the combination. The evidence in Attard 2009 and Ryan 2011, along with the Phase II studies, show the increased clinical efficacy of the combination over AA monotherapy. The exception to the weight of this evidence is McKay 2019 which stands as an outlier.

[255] The Phase I and II studies, as per Attard 2008 and 2009 with Attard 2010, showed that AA was safe, and that AA with low dose corticosteroids provided durable secondary tumour response. Danila 2010 which studied AA and PN supported those conclusions. These studies and publications taught physicians that glucocorticoids as a class contributed to anti-cancer effects when used in combination with AA.

[256] The Defendants challenge whether any conclusion can be made from these Phase II and Phase III (de Bono 2011, Ryan 2013 and Ryan 2015) AA publications with respect to PN but rely on prior art studies of a similar type to establish obviousness.

[257] The Court has previously dealt with the different opinions of Drs. Ballman and McKeague and this Court's acceptance of Dr. Ballman's.

[258] The Defendants know or ought to know that PN has an anti-cancer effect in combination with AA. Its efforts to advance the side effects and palliation activities of PN do not relieve it of the consequences of infringement arising from its "holding out" contained in the Product Monograph. It will advertise, and sell its Products with the intent that the AA and PN in combination will be used to treat prostate cancer. Such infringement would not occur if the Defendants did not put out a Product Monograph, obtain regulatory approval and sell its Products.

[259] The Indications and Use section of the Product Monograph is of importance to a physician when determining the use to be made of a product. The indicated use is consistent with the Asserted Claims.

[260] The Defendants will be directing the use of AA and PN for the treatment of mCRPC which therefore constitutes inducing infringement of the Asserted Claims in 422 Patent, and HSPC in respect of PMS and Dr. Reddy's.

IX. Conclusion

[261] For these Reasons, the Plaintiffs' action will be dismissed. The counterclaim will likewise be dismissed. The invention is obvious/obvious to try. The 422 Patent is and has been invalid.

[262] No specific order need be made with respect to Infringement but is referred to in the Judgment for completeness.

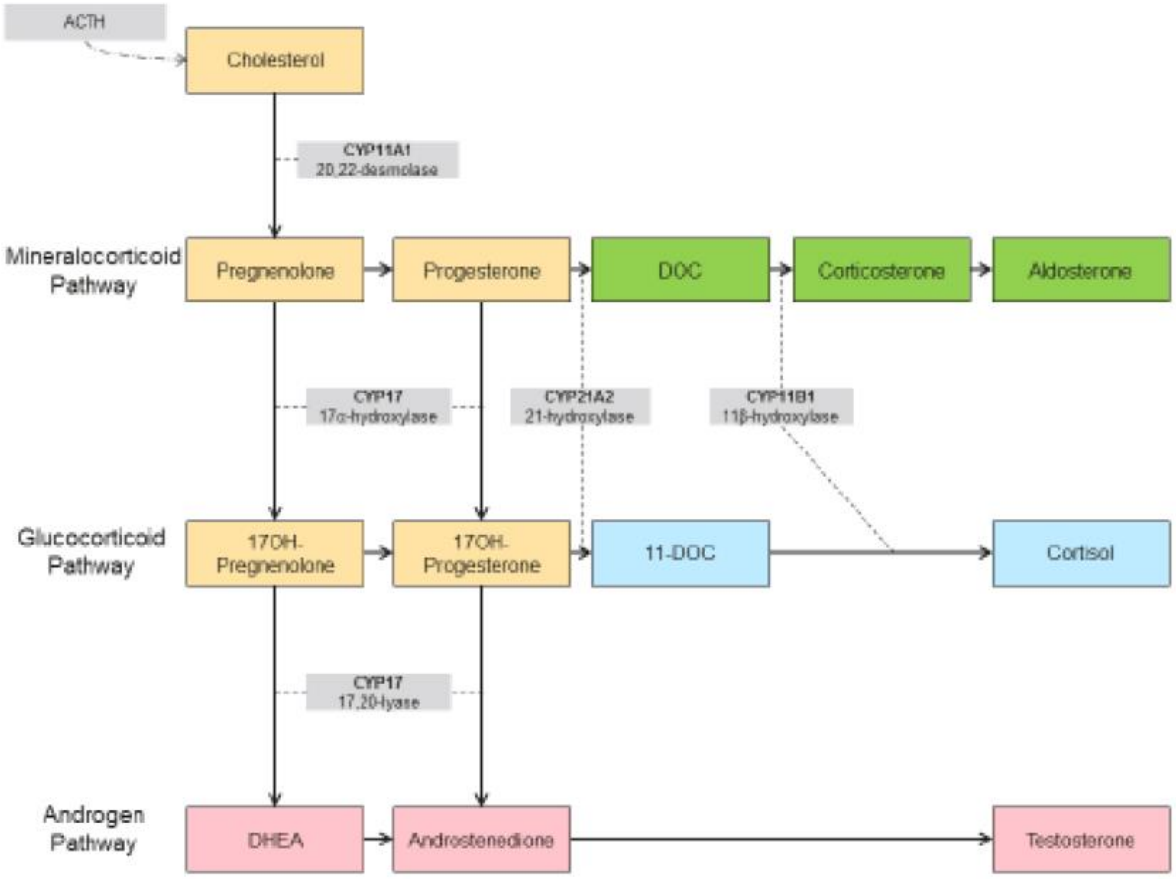
[263] These Reasons are confidential. The parties will have seven (7) days to make submissions as to the portions of these Reasons which should remain confidential. A public version of these Reasons will then follow.

[264] The Defendants are entitled to their costs. A case conference will be held to establish the procedure to be followed with respect to costs including issues of lump sum, the scale to be used and any issues of apportionment as between the Defendants.

"Michael L. Phelan"
Judge

Ottawa, Ontario
January 14, 2021

Schedule A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Aldosterone
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CYP21A2
21-hydroxylase
CYP11B1
11β-hydroxylase
Glucocorticoid Pathway
17OH-Pregnenolone
17OH-Progesterone
11-DOC
Cortisol
CYP17
17,20-lyase
Androgen Pathway
DHEA
Androstenedione
Testosterone

FEDERAL COURT

SOLICITORS OF RECORD

DOCKET:	T-84-19
STYLE OF CAUSE:	JANSSEN INC, JANSSEN ONCOLOGY, INC AND BTG INTERNATIONAL LTD v APOTEX INC
AND DOCKET:	T-978-19
STYLE OF CAUSE:	JANSSEN INC, JANSSEN ONCOLOGY, INC AND BTG INTERNATIONAL LTD v DR REDDY'S LABORATORIES LTD AND DR REDDY'S LABORATORIES, INC
AND DOCKETS:	T-182-19 AND T-1893-19
STYLE OF CAUSE:	JANSSEN INC, JANSSEN ONCOLOGY, INC AND BTG INTERNATIONAL LTD v PHARMASCIENCE INC
PLACE OF HEARING:	HELD BY VIDEOCONFERENCE BETWEEN OTTAWA, ONTARIO AND TORONTO, ONTARIO (COURT IN OTTAWA, AND COUNSEL IN TORONTO AND OTTAWA).
DATE OF HEARING:	OCTOBER 26-29, 2020 NOVEMBER 2-5, 2020 NOVEMBER 9-10 AND 12, 2020 NOVEMBER 16-19, 2020 NOVEMBER 26 AND 27, 2020
REASONS FOR JUDGMENT:	PHELAN J.
CONFIDENTIAL REASONS FOR JUDGMENT ISSUED:	JANUARY 6, 2021
PUBLIC REASONS FOR JUDGMENT ISSUED:	JANUARY 14, 2021

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