Federal Court Cour fédérale

Date: 20220823

Docket: T-1441-20
T-558-22

Citation: 2022 FC 1218

Ottawa, Ontario, August 23, 2022

PRESENT: The Honourable Mr. Justice Manson

BETWEEN:

JANSSEN INC. and JANSSEN PHARMACEUTICA N.V.

Plaintiffs

and

PHARMASCIENCE INC.

Defendant

PUBLIC JUDGMENT AND REASONS

(Confidential Judgment and Reasons issued August 23, 2022)

I. Introduction

[1] This proceeding involves two patent infringement actions – Court File Nos. T-1441-20 and T-558-22 – pursuant to subsection 6(1) of the *Patented Medicines (Notice of Compliance) Regulations*, SOR/93-133 (the "*Regulations*").

II. Background

A. *The Parties*

[2] The Plaintiffs are Janssen Inc., a corporation headquartered in Toronto, and Janssen Pharmaceutica N.V., a corporation headquartered in Belgium (collectively, "Janssen"). Janssen Inc. is a "first person" as defined in the *Regulations*, and Janssen Pharmaceutica N.V. is a party to this action pursuant to subsection 6(2) of the *Regulations* as the registered owner of Canadian Patent No. 2,655,335 (the "335 Patent").

[3] The Defendant, Pharmascience Inc. ("Pharmascience" or "PMS"), is a generic pharmaceutical company headquartered in Montréal. Pharmascience is a "second person" in accordance with the *Regulations*.

B. *Technical Background*

(1) Schizophrenia and Related Disorders

[4] Schizophrenia is a debilitating, lifelong disease estimated to afflict over 300,000 Canadians. Symptom onset typically manifests as a psychotic breakdown, and often occurs when the afflicted individual is in their early to mid-twenties.

[5] Schizophrenia is characterized by "positive" symptoms (such as hallucinations, delusions, and disorganized behaviour) and "negative" symptoms (such as apathy, lack of motivation, and social withdrawal). Diagnosis takes place once symptoms persist for at least six

months after onset and must include the presence of at least two characteristic symptoms for a significant portion of time during a one-month period.

[6] Schizophreniform disorder requires the presence of characteristic symptoms for at least one month, but less than six months. Schizoaffective disorder requires similar diagnostic criteria to schizophrenia with an additional mood element, such as major depressive episodes, manic episodes, or both. Unless otherwise indicated, references to “schizophrenia” in these reasons should be understood to mean schizophrenia, schizophreniform disorder, and schizoaffective disorder.

[7] The underlying mechanism causing schizophrenia symptoms is abnormal dopamine functioning in certain parts of the brain. Since the 1970s, researchers have been aware that effective antipsychotic medications act by blocking dopamine at the D2 receptor.

(2) Treatment of Schizophrenia

[8] Antipsychotic drugs are the cornerstone of schizophrenia treatment and management. They can be broken down into two classes: (1) typical (first generation) antipsychotics; and (2) atypical (second generation) antipsychotics.

[9] Typical (first generation) antipsychotics block D2 receptors in the brain and work well against positive symptoms of schizophrenia. However, they are also associated with a high incidence of severe adverse side effects called extrapyramidal symptoms, which typically

involve motor control issues (such as muscle spasms, muscle rigidity, restlessness, and jerky movements).

[10] Atypical (second generation) antipsychotics entered the market in the 1990s, and act on both dopamine and serotonin receptors. Atypical antipsychotics are associated with a far lower incidence of extrapyramidal symptoms.

[11] As stated above, schizophrenia is incurable and requires life long management with antipsychotic medications. Adherence to a treatment regimen is critical. Many schizophrenia patients take oral antipsychotics and are responsible for administering their own medication. A leading cause of relapse is non-adherence, where patients do no take their antipsychotic medication as prescribed, or at all. Rates of non-adherence amongst individuals with schizophrenia are very high.

[12] One strategy to ensure treatment adherence is the use of long-acting formulations of antipsychotics. One type of long-acting formulation is intramuscular injections of antipsychotic drugs, known as “depot formulations” or “long-acting injectables.” Once injected, the drug releases from the injection site slowly, providing the patient with prolonged drug exposure.

C. *The Invention Story*

[13] In the early 1990s, Janssen started working on a long-acting injectable paliperidone formulation for the treatment of schizophrenia. Around 2003, a global research team to support

this development was labelled the Paliperidone Palmitate Compound Development Team (PP CDT).

[14] The primary goals of the PP CDT were to optimize the formulation of the paliperidone palmitate injection for monthly delivery; evaluate the safety and efficacy of paliperidone palmitate for the treatment of schizophrenia and other disorders; and to develop dosing regimens for the drug that would achieve regulatory approval.

[15] Dr. An Vermeulen, a pharmacometrician at Janssen, was actively involved in the development of the dosage regimen for paliperidone palmitate. Initial multi-dose studies conducted at Janssen indicated that, among other things, once monthly injections patients would only reach steady-state plasma concentrations of paliperidone after four to five months. In 1999, Dr. Vermeulen designed a Phase I study, BEL-7, which compared two different loading dose regimens: (1) administering a double dose on Day 1 with monthly dosing thereafter; and (2) administering the same dose on Day 1 and Day 8 with monthly dosing thereafter. All doses were administered intramuscularly in the gluteal muscle. The BEL-7 study showed that the second loading dose regimen with fixed doses on Day 1 and Day 8 and monthly doses thereafter resulted in steady-state plasma concentrations within the first month.

[16] Following Phase I clinical trials, Dr. Vermeulen developed a population pharmacokinetic model to assist in making informed dosing decisions and support dosing regimen selections. In 2003, Janssen moved forward with the Phase II study SCH-201 based on the results of the BEL-7 study and Dr. Vermeulen’s modeling. The SCH-201 study tested fixed doses of 50 and 100

milligram equivalent (mg-eq.) administered in the gluteal muscle on Days 1, 8, and monthly thereafter.

[17] Based on the success of SCH-201, Janssen designed two Phase III studies – PSY-3003 and PSY-3004 – to investigate fixed doses of 25, 50, 100, and 150 mg-eq. administered on Days 1, 8, and monthly thereafter into the gluteal muscle. These studies were conducted from December 2004 to March 2006, and June 2005 to June 2006, respectively.

[18] In April 2006, Dr. Srihari Gopal joined Janssen as a Project Physician on the Clinical Team subgroup of the PP CDT. He was assigned responsibility for ongoing paliperidone palmitate Phase III clinical trials. At this time, the PSY-3003 and PSY-3004 studies were either complete or nearing completion. The results of these studies were unexpectedly disappointing, and led to the creation of a special task force, including Drs. Vermeulen and Gopal, to troubleshoot problems identified following the Phase III studies and propose improvements to the dosing regimen.

[19] To assist in revising the dosing regimen, Dr. Vermeulen developed a new population pharmacokinetic model using clinical data from over 1,200 patients. She used this model to evaluate several different dosing regimens by simulating the plasma concentrations of a virtual, representative patient population.

[20] The task force eventually identified a “treatment by country” interaction in patients from the United States that was determined to be the result of high body mass index. The task force then focused on adjusting the dose regimen for future trials to overcome the issue.

[21] In 2006, Dr. Vermeulen moved to a new position within Janssen. Dr. Mahesh Samtani took over her role on the PP CDT in February 2007. He was tasked with developing a new population pharmacokinetic model for Janssen’s long-acting injectable paliperidone palmitate formulation.

[22] In February and December 2007, advisory board meetings were held with representatives of Janssen (including Drs. Gopal (attended both meetings), Vermeulen (attended the February meeting), and Samtani (attended the February meeting)) and external advisors (including Dr. Ereshefsky (attended the December meeting)). The objectives of the meetings were to review and obtain feedback on the clinical trial data and planned submissions to regulatory authorities. At that time, the proposed dosing regimen included: 1) a 150 mg-eq. dose administered in the deltoid muscle on Day 1 of treatment, 2) a second dose in the range of 25 to 150 mg-eq. in either the deltoid or gluteal muscle starting on Day 8, and 3) monthly doses thereafter.

[23] The advisors were of the view that the use of a 150 mg-eq. dose for most of the patients was a risk and a more acceptable regimen would be to start with 100 mg-eq. The reluctance to accept a 150 mg-eq. starting dose was due to two concerns: 1) safety (overdosing) concerns and 2) the acceptability of regulatory authorities. In light of the feedback, Janssen went forward with

an initial new drug application that had a 100 mg-eq. starting dose, including other refinements to the regimen.

[24] Dr. Samtani built a new model using data from over 1,400 patients, comprising 15,000 samples from Phase I, II, and III studies. The development and validation took approximately six months, and took into account a wide range of covariates and paliperidone palmitate's absorption and elimination process. Once complete, simulations were ran to guide optimization of the paliperidone palmitate-dosing regimen.

[25] Dr. Samtani used his model to establish a dosing regimen comprised of loading doses of 150 mg-eq. on Day 1 and 100 mg-eq. on Day 8 injected into the deltoid muscle, and maintenance doses of 75 mg-eq. monthly thereafter injected into either the deltoid or gluteal muscle. Based on modeling, simulation, and the results of a further Phase III study PSY-3007, the team was confident that this dosing regimen was safe and effective; did not require oral supplementation; brought patients to steady-state plasma concentration within one week; and matched the plasma concentrations of patients taking 6 mg dose of INVEGA®, an extended release oral tablet of paliperidone.

[26] Dr. Samtani also used his model to develop recommended flexible tolerance intervals for the timing of the second loading dose and subsequent maintenance dose injections, or "dosing windows." He determined that dosing windows of ± 2 days for the second loading dose and ± 7 days for the monthly maintenance doses would maintain therapeutic plasma concentrations without affecting safety and efficacy. Based on modeling and clinical data, Dr. Samtani also

determined the appropriate downward dose adjustments for renally impaired patients – a 100 mg-eq. dose on Day 1 followed by a 75 mg-eq. dose on Day 8, both in the deltoid, and monthly doses thereafter of 50mg-eq. in either the deltoid or the gluteal muscle.

[27] While Janssen did not receive the results of the PSY-3007 study until after December 19, 2007 (the first priority date for the 353 Patent), Dr. Samtani had developed this regimen using his population pharmacokinetic model and confirmed the safety and efficacy of the regimen (at least in part) using the PSY-3007 results.

D. *The 335 Patent*

[28] The 335 Patent is titled "Prolonged-Release Injectable Suspensions of Paliperidone Palmitate and Dosage Forms and Delivery Systems Incorporating Same."

[29] The 335 Patent issued from an application filed in Canada on December 17, 2008, claiming priority from United States Patent Application No. 61/014,918, filed on December 19, 2007. The 335 Patent was laid open on June 19, 2009, issued on September 6, 2016, and has not expired.

[30] The 335 Patent contains 63 claims – each of which is asserted in the two actions in this proceeding. Claims 1, 2, 17, 18, 33, 34, 49, and 50 are independent claims.

[31] The 335 Patent relates to dosing regimens for long-acting injectable paliperidone palmitate formulations for treatment of schizophrenia and related disorders, and teaches a dosing

regimen that ensures an optimum plasma concentration-time profile for treating patients with paliperidone. The inventors targeted a plasma concentration exposure range of 7.5 to 40 ng/mL of paliperidone after injection to ensure efficacy and minimize adverse side effects.

[32] In order to rapidly achieve therapeutic blood plasma concentrations, the 335 Patent teaches a "loading dose" regimen, wherein a specific dose is administered on Day 1 and a different specific dose is administered on Day 8 – both in the deltoid muscle. The "loading dose" regimen is followed by a "maintenance dose" regimen comprised of doses of paliperidone palmitate administered monthly thereafter, in either the deltoid or the gluteal muscle.

[33] The dosing regimen incorporates "dosing windows" of ± 2 days for the second loading dose, and ± 7 days for the monthly maintenance doses.

[34] The claims of the 335 Patent break down into four sets:

i. Claims 1 to 16 relate to prefilled syringes adapted for administration according to the claimed dosing regimens;

ii. Claims 17 to 32 relate to a use of a "dosage form" according to the claimed dosing regimens;

iii. Claims 33 to 48 relate to use of paliperidone as paliperidone palmitate in the manufacture/preparation of a "medicament" adapted for administration according to the claimed dosing regimen; and

iv. Claims 49 to 63 relate to a “dosage form” adapted for administration according to the claimed dosage regimens.

[35] The claimed dosing regimen for non-renally impaired psychiatric patients in need of treatment for schizophrenia is defined in claims 1, 17, 33, and 49:

i. A first loading dose of 150 mg-eq. of paliperidone palmitate administered into the deltoid muscle on Day 1 of treatment;

ii. A second loading dose of 100 mg-eq. of paliperidone palmitate administered into the deltoid on Day 8 ± 2 days; and

iii. Maintenance doses of 75 mg-eq. of paliperidone palmitate administered into the deltoid or gluteal muscle monthly ± 7 days after the second injection.

[36] The claimed dosing regimen for renally impaired patients, as defined in claims 2, 18, 34, and 50 follows the same dosing schedule, dosing windows, and injection sites, but with loading doses of 100 mg-eq. and 75 mg-eq., and maintenance doses of 50 mg-eq.

E. *INVEGA SUSTENNA®*

[37] The 335 Patent is listed on the Patent Register maintained by the Minister of Health pursuant to the *Regulations* in respect of Janssen’s paliperidone palmitate suspension, marketed

under the brand name INVEGA SUSTENNA®, in dosage strengths of 50 mg/0.5 mL (*i.e.* 50 mg-eq.), 75 mg/0.75 mL, 100 mg/1 mL, and 150 mg/1.5 mL.

[38] The product monograph for INVEGA SUSTENNA® sets out dosing regimens falling within the claims of the 335 Patent.

F. *Litigation History*

(1) Court File No. T-353-18: Janssen Inc. v. Teva Canada Ltd.

[39] Janssen has previously asserted claims 1 to 48 of the 335 Patent against Teva Canada Ltd. in Court File No. T-353-18 (*Janssen Inc. v. Teva Canada Ltd.*, 2020 FC 593 [*Teva Paliperidone*]).

[40] In *Teva Paliperidone*, I determined, among other things, the Person of Ordinary Skill in the Art (POSITA), the Common General Knowledge, and the construction of claims 1 to 48 of the 335 Patent – the details of which will be set out in the relevant sections below.

[41] While the appeal of *Teva Paliperidone* is currently pending, the POSITA and construction of claims 1 to 48 of the 335 Patent are not at issue in these proceedings.

(2) Court File No. T-455-20: Janssen Inc. v. Pharmascience Inc.

[42] On February 28, 2020, Pharmascience served a Notice of Allegation and Detailed Statement in respect of its Abbreviated New Drug Submission (ANDS) No. 236094 in regards to

the 335 Patent and seeking approval to market and sell in Canada 50, 75, 100, and 150 mg-eq. doses of a proposed pms-PALIPERIDONE PALMITATE product, a generic version of Janssen's INVEGA SUSTENNA® product.

[43] In response, Janssen commenced an infringement action under subsection 6(1) of the *Regulations* on April 8, 2020 in Court File No. T-455-20. On October 2, 2020, the action in respect to ANDS No. 236094 was discontinued on consent.

(3) Court File No. T-1441-20: Janssen Inc. v. Pharmascience Inc.

[44] On October 16, 2020, Pharmascience served a Notice of Allegation and Detailed Statement in respect of its ANDS No. 244641 in regards to the 335 Patent and seeking approval to market and sell in Canada [redacted] doses of its proposed pms-PALIPERIDONE PALMITATE, a generic version of Janssen's INVEGA SUSTENNA® product.

[45] Pharmascience alleges that the 335 Patent is invalid or void and would not be infringed by the making, constructing, using, or selling of a proposed pms-PALIPERIDONE PALMITATE as set out in ANDS No. 244641.

[46] In response, Janssen commenced an action (File No. T-1441-20) against Pharmascience pursuant to subsection 6(1) of the *Regulations* on November 27, 2020. Janssen is seeking:

a. A declaration that the making, constructing, using, or selling of pms-PALIPERIDONE PALMITATE by Pharmascience in accordance with ANDS

No. 244641 would infringe claims 1 to 63 of the 335 Patent, directly and/or indirectly;

b. A permanent injunction restraining Pharmascience (as well as its subsidiaries and affiliates) from:

   i. Making, constructing, using, or selling the pms-PALIPERIDONE PALMITATE in Canada;

   ii. Offering for sale, marketing, or having the pms-PALIPERIDONE PALMITATE marketed in Canada;

   iii. Importing, exporting, distributing, or having the pms-PALIPERIDONE PALMITATE distributed in Canada; and

   iv. Otherwise infringing or inducing others to infringe the 335 Patent.

c. If Pharmascience makes, constructs, uses, or sells the pms-PALIPERIDONE PALMITATE before the expiry of the 335 Patent, damages or an accounting of Pharmascience's profits, as Janssen may elect, resulting from Pharmascience's infringing activities in respect of the 335 Patent;

d. Janssen's costs of this action; and

e. Any other relief that this Honourable Court deems just.

[47] On January 26, 2021, Pharmascience brought a motion for summary trial on the grounds that the pms-PALIPERIDONE PALMITATE, made in accordance with ANDS No. 244641,

does not contain an essential element (*i.e.* the 75 mg-eq. dose) of any of the 63 claims of the 335 Patent and, therefore, cannot infringe the 335 Patent.

[48] In *Janssen Inc. v. Pharmascience Inc.*, 2022 FC 62 [*PMS Paliperidone*], I found that Janssen had shown, on a balance of probabilities, that Pharmascience's proposed pms-PALIPERIDONE PALMITATE in accordance with ANDS No. 244641 will induce infringement of the 335 Patent. More specifically, based on the evidence, there appear to be several instances in the product monograph of the proposed pms-PALIPERIDONE PALMITATE that would influence prescribers to prescribe the claimed dosing regimen leading to direct infringement of the 335 Patent.

[49] Thus, Janssen's action was not dismissed and was allowed to proceed on Pharmascience's defence of alleged invalidity as described herein.

[50] The appeal of the *PMS Paliperidone* summary trial is currently pending.

[51] Since all 63 claims of the 335 Patent are at issue in Court File No. T-1441-20, claims 49 to 63 have been construed – the details of which will be set out in the relevant section below.

(4) Court File No. T-553-22: Janssen Inv. v. Pharmascience Inc.

[52] On January 29, 2022, Pharmascience served a Notice of Allegation and Detailed Statement in respect of its ANDS No. 251767 in regards to the 335 Patent and seeking approval

to market and sell in Canada [redacted] of its proposed pms-PALIPERIDONE PALMITATE, a generic version of Janssen's INVEGA SUSTENNA® product.

[53] In the Statement of Claim, Janssen asserts that the letter served on them was not a proper Notice of Allegation as Pharmascience failed to comply with the *Regulations*. However, this is not an issue in these proceedings.

[54] Pharmascience alleges that the 335 Patent is invalid or void, but does not contest infringement by the making, constructing, using, or selling of a proposed pms-PALIPERIDONE PALMITATE as set out in ANDS No. 251767.

[55] In response, Janssen commenced an action (Court File No. T-558-22) against Pharmascience pursuant to subsection 6(1) of the *Regulations* on March 14, 2022. Janssen is seeking:

a. A declaration that the making, constructing, using, or selling of pms-PALIPERIDONE PALMITATE by Pharmascience in accordance with ANDS No. 251767 would infringe claims 1 to 63 of the 335 Patent, directly and/or indirectly;

b. A permanent injunction restraining Pharmascience (as well as its subsidiaries and affiliates) from:

    i. Making, constructing, using, or selling the pms-PALIPERIDONE PALMITATE in Canada;

ii. Offering for sale, marketing, or having the pms-PALIPERIDONE PALMITATE marketed in Canada;

iii. Importing, exporting, distributing, or having the pms-PALIPERIDONE PALMITATE distributed in Canada; and

iv. Otherwise infringing or inducing others to infringe the 335 Patent.

c. If Pharmascience makes, constructs, uses, or sells the pms-PALIPERIDONE PALMITATE before the expiry of the 335 Patent, damages or an accounting of Pharmascience's profits, as Janssen may elect, resulting from Pharmascience's infringing activities in respect of the 335 Patent;

d. Janssen's costs of this action; and

e. Any other relief that this Honourable Court deems just.

III. Issues

[56] As stated above, at the motion for summary trial dealing solely with the issue of infringement, Janssen's action was not dismissed, a finding of infringement was made, and this action has proceeded on the basis Pharmascience's defence of alleged invalidity of the 335 Patent.

[57] The Parties have filed a Joint Statement of Issues:

i. Whether any of the claims of the 335 Patent are invalid on the basis of obviousness, pursuant to section 28.3 of the *Patent Act*, RSC 1985, c P-4; and

ii. Whether any of the claims of the 335 Patent are invalid on the basis of lack of patentable subject matter (*i.e.* as a method of medical treatment) under section 2 of the *Patent Act*.

IV. Analysis

A. *The Experts and Fact Witnesses*

(1) Janssen's Fact Witnesses

(a) *An Vermeulen, PhD*

[58] Dr. Vermeulen is a named co-inventor of the 335 Patent. She is currently the Clinical Pharmacology and Pharmacometrics Therapeutic Area Head for Immunology at Janssen.

[59] Dr. Vermeulen received her PhD in Pharmaceutical Sciences from the University of Ghent, with a focus on pharmacokinetics.

[60] Dr. Vermeulen was a credible witness and gave evidence on her work in the development of pharmacokinetic models to guide decision-making, design clinical trials, and support dose regimen selection and adaptation of the formulation and dosing regimens for Janssen's paliperidone palmitate injectable as described above in the invention story.

(b) *Srihari Gopal, MD*

[61] Dr. Gopal is a named co-inventor of the 335 Patent. Though no longer employed by or associated with Janssen, at the time of signing his affidavit he was Senior Director (Head of Development, Psychiatry) at Janssen Research & Development LLC.

[62] Dr. Gopal obtained his medical degree from Rutgers University before completing two medical residencies: one in association with the Department of Surgery at the University of Illinois, College of Medicine and the other in association with the Department of Family Medicine at the Baylor College of Medicine in Texas. Dr. Gopal also has a Masters of Health Science in association with the Clinical Research Training Program at Duke University in North Carolina.

[63] Dr. Gopal was a credible witness and gave evidence about his role in the development of the paliperidone palmitate one-month long-acting injectable formulation, as well as his understanding of the studies completed before his employment at Janssen. Dr. Gopal became involved with the PP CDT during the Phase III trials as described above in the invention story.

[64] On consent, the final paragraph of Dr. Gopal's affidavit was removed in response to an objection raised by Pharmascience.

(c) *Mahesh Samtani, PhD*

[65] Dr. Samtani is a named co-inventor of the 335 Patent. He is currently Senior Director, US Pharmacometrics Head at Janssen.

[66] Dr. Samtani received his PhD in Pharmaceutical Science from the State University of New York. A portion of his PhD thesis was on pharmacokinetic and pharmacodynamic modeling of aqueous suspensions of a corticosteroid with long-acting properties.

[67] Dr. Samtani was a credible witness and gave evidence about his role in the development of a population pharmacokinetic model that would be suitable for submissions to regulatory authorities and would aid in optimizing the dosing regimen for paliperidone palmitate as described above in the invention story.

(2) Pharmascience's Fact Witnesses

(a) *Horatiu Lazar*

[68] Mr. Lazar is a Marketing and Sales Data Analyst at Pharmascience. He described how the IGVIA (formerly, IMS) data (which provides pharmaceutical sales and prescription data for paliperidone palmitate products from 2021) cited in Dr. Jeffries expert report was prepared.

[69] Mr. Lazar was not examined and his affidavit was entered into evidence as read.

(b) *Nathaniel Frank-White*

[70] Mr. Frank-White is a Records Request Processor at the Internet Archive, which provides the Wayback Machine service. He provided screenshots of a Johnson & Johnson webpage that linked to webcasts and documents of public conferences and events held by the company from June 7, 2007 to January 22, 2008, including the Credit Suisse investors meeting transcript.

[71] Mr. Frank-White was not examined and his affidavit was entered into evidence as read.

(3) Janssen's Expert Witnesses

(a) *Dr. Pierre Chue*

[72] Dr. Chue is a Medical Doctor with specialized training in the field of psychiatry. He holds several clinical, research, and teaching positions with Alberta Health Services and the University of Alberta. Dr. Chue's practice focuses on the treatment of adult patients with mental illness, including schizophrenia and schizoaffective disorder.

[73] Dr. Chue obtained his Bachelor of Medicine, Bachelor of Surgery (MBBCh) from the Welsh National School of Medicine.

[74] Dr. Chue was qualified as an expert in the diagnosis and treatment of schizophrenia and schizoaffective disorder. This expertise includes the clinical use of injectable depot medications,

such as paliperidone palmitate (*i.e.* INVEGA SUSTENNA®), as well as oral antipsychotic medications.

[75] Pharmascience raised a preliminary objection to portions of Dr. Chue's testimony under Rule 248 of the *Federal Court Rules*, SOR/98-106. Pharmascience objected to any testimony regarding the prescribing practices of Canadian physicians because a Janssen corporate representative had previously refused to answer whether they had any information about the prescribing practices of Canadian physicians during discovery.

[76] As I have previously ruled in related proceedings, testimony regarding the practices and knowledge of other physicians is hearsay, neither reliable nor necessary, and, as such, given little to no weight (*Teva Paliperidone* at paragraph 52).

[77] Dr. Chue testified to the issues of obviousness and method of medical treatment. Dr. Chue was somewhat obstructionist during cross-examination, and did not give straightforward answers to many simple questions. Nevertheless, the weight of his evidence, when of value, is considered below.

(b) *Larry Ereshefsky, PharmD*

[78] Dr. Ereshefsky is a Clinical Pharmacologist and Certified Psychiatric Pharmacist with over 40 years of experience as a clinician, scientist, and investigator in developing treatments and clinical methodologies for neurodegenerative and psychiatric disorders, including schizophrenia.

[79] Dr. Ereshefsky obtained his PharmD from the University of Southern California and completed his residency in psychiatric pharmacy/psychopharmacology at the University of Southern California – Los Angeles County Medical Center. Now retired, he was a Professor of Pharmacy, Psychiatry, and Pharmacology at the University of Texas, teaching courses in psychiatric therapeutics and clinical pharmacology.

[80] As Associate Director of the Clinical Research Unit at San Antonio State Hospital, Dr. Ereshefsky oversaw the clinical care and conduct of numerous clinical trials in the development of atypical antipsychotics and new therapies for schizophrenia and other disorders.

[81] Dr. Ereshefsky was qualified as an expert in:

i. Clinical pharmacology, particularly in the clinical pharmacology of antipsychotic drugs;

ii. Evaluating the pharmacokinetics, pharmacodynamics, bioequivalence, drug-drug interactions, and pharmacogenetics of antipsychotic drugs, including long-acting injectable (depot) antipsychotic drugs;

iii. The clinical use of antipsychotic drugs, including designing, implementing, monitoring, and modifying treatment plans for patients using antipsychotic dugs (including long-acting injectable antipsychotic drugs) for treatment pf psychiatric disorders, including schizophrenia, schizoaffective disorder, and schizophreniform disorder;

iv. Clinical trial design and implementation, including clinical trials for drugs used in the treatment of psychiatric disorders, including schizophrenia, schizoaffective disorder, and schizophreniform disorder;

v. Translational psychopharmacology, including the evaluation of preclinical (animal) data and models and the extrapolation of preclinical date to predict pharmacokinetic and pharmacodynamic parameters in humans; and

vi. The evaluation of toxicology and safety signals, including in translating preclinical and clinical trial data into design strategies incorporating patient assessments/biomarkers and in exploring exposure limits.

[82] Dr. Ereshefsky testified to the issues of obviousness and method of medical treatment. He suffered some credibility issues in providing several unreasonable opinions, related to evidence on the issue of obviousness, as discussed in more detail below.

(4) Pharmascience's Expert Witnesses

(a) *Joel Jeffries, MD*

[83] Dr. Jeffries was appointed as Staff Psychiatrist at the Centre for Addiction and Mental Health from 1998 until May 2021, when he retired from active clinical practice. Among other teaching roles, Dr. Jeffries has been an Associate Professor of Psychiatry and Pharmacy at the University of Toronto since 1978, and claims more than 50 years of experience in psychiatry. Dr. Jeffries received his medical degree from the University of Dublin.

[84] Dr. Jeffries was qualified as an expert in the field of psychiatry, including in the diagnosis, monitoring, and treatment of patients with schizophrenia and related disorders, including long-acting injectables and depot formulations. He is also an expert in the prescribing practices of psychiatrists and the standard of practice of psychiatrists and physicians treating patients with schizophrenia and related disorders.

[85] Dr. Jeffries provided his opinion on the issue of method of medical treatment. He suffered some credibility issues, having provided inconsistent statements and sometimes seemed confused or unable to follow relatively straight-forward questions. Dr. Jeffries has also never prescribed INVEGA SUSTENNA®. As stated above for Dr. Chue's testimony, any testimony provided by Dr. Jeffries reflecting other physicians prescribing practices gathered from discussions with colleagues is hearsay and is given little or no weight.

(b) *Pardeep Gupta, PhD*

[86] Dr. Gupta is a Professor of Pharmaceutics and Burroughs Wellcome Chair in the Department of Pharmaceutical Sciences at University of the Sciences in Philadelphia. He is also the Director of Industrial Pharmacy Laboratory at Philadelphia College of Pharmacy, University of the Sciences in Philadelphia. He teaches on the topics of injectable and non-injectable pharmaceutical formulations, drug diffusion, controlled drug delivery, pharmaceutical rate processes, drug stability, bioavailability and pharmacokinetics.

[87] Dr. Gupta received his PhD in Pharmaceutics and Physical Chemistry from the University of Wisconsin – Madison. His research was focussed on study of the biological

variables that affect bioavailability of drugs and his graduate education in pharmaceutical sciences involved extensive course work and research projects in the area of drug formulation, chemical modifications of drugs and pharmacokinetics.

[88] Dr. Gupta was qualified as an expert in the field of drug dissolution, drug formulation, and drug delivery systems, including nanoparticle-based injectables. He is also an expert in the bioavailability and pharmacokinetic trials and is familiar with pharmacokinetic modelling.

[89] Dr. Gupta provided his opinion on the issue of obviousness. He suffered some credibility issues in failing to agree to or admit simple, straightforward propositions. Dr. Gupta has also never conducted or designed a clinical trial or pharmacokinetic trial in humans.

B. *Claim Construction*

[90] Claim construction is a matter of law for the Court (*Whirlpool Corp.v. Camco Inc.*, 2000 SCC 67 at paragraph 61). Where the judge can construe the patent as it would be understood by a skilled person, expert evidence is not required (*Pfizer Canada Inc. v. Canada (Minister of Health)*, 2007 FC 446 at paragraphs 25, 35, and 36; *Excalibre Oil Tools Ltd. v. Advantage Products Inc.*, 2016 FC 1279 at paragraph 119).

[91] The principles of claim construction were summarized by the Federal Court of Appeal in *Tearlab Corporation v. I-Med Pharma Inc.*, 2019 FCA 179 at paragraphs 30 to 34:

> [30] The general principles of claim construction are now well established and were set out by the Supreme Court in three cases (*Whirlpool* at paras. 49-55; *Free World Trust v. Électro Santé Inc.*,

2000 SCC 66, [2000] 2 S.C.R. 1024 at paras. 31-67 [*Free World Trust*]; *Consolboard Inc. v. MacMillan Bloedel (Sask.) Ltd*., 1981 CanLII 15 (SCC), [1981] 1 S.C.R. 504 at p. 520 [*Consolboard*]). These principles can be summarized as follows.

[31] The *Patent Act* promotes adherence to the language of the claims, which in turn promotes fairness and predictability (*Free World Trust* at paras. 31(a), (b) and 41). The words of the claims must, however, be read in an informed and purposive way (at para. 31(c)), with a mind willing to understand (at para. 44). On a purposive construction, it will be apparent that some elements of the claimed invention are essential while others are non-essential (at para. 31(e)). The interpretative task of the court, in claim construction, is to separate and distinguish between the essential and the non-essential elements, and to give the legal protection to which the holder of a valid patent is entitled only to the essential elements (at para. 15).

[32] To identify these elements, the claim language must be read through the eyes of a POSITA, in light of the latter's common general knowledge (*Free World Trust* at paras. 44-45; see also *Frac Shack* at para. 60; *Whirlpool* at para. 53). As noted in *Free World Trust*:

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

[33] Claim construction requires that the disclosure and the claims be looked at as a whole "to ascertain the nature of the invention and methods of its performance, … being neither benevolent nor harsh, but rather seeking a construction which is reasonable and fair to both patentee and public" (*Consolboard* at p. 520; see also *Teva Canada Ltd. v. Pfizer Canada Inc*., 2012 SCC 60, [2012] 3 S.C.R. 625 at para. 50). Consideration can thus be given to the patent specifications to understand what was meant by the words in the claims. One must be wary, however, not to use these so as "to enlarge or contract the scope of the claim as written and … understood" (*Whirlpool* at para. 52; see also *Free World Trust* at

> para. 32). The Supreme Court recently emphasized that the focus of the validity analysis will be on the claims; specifications will be relevant where there is ambiguity in the claims (*AstraZeneca Canada Inc. v. Apotex Inc*., 2017 SCC 36, [2017] 1 S.C.R. 943 at para. 31; see also *Ciba* at paras. 74-75).
>
> [34] Finally, it is important to stress that claim construction must be the same for the purpose of validity and for the purpose of infringement (*Whirlpool* at para. 49(b)).

[92] The relevant date for construing the claims is the publication date: June 19, 2009.

[93] As stated above, the construction of all 63 claims of the 335 Patent and the POSITA have been previously determined and are not at issue in these proceedings.

[94] The essential elements of claim 1 are (*Teva Paliperidone* at paragraph 145):

i. Prefilled syringes containing a depot formulation of paliperidone as paliperidone palmitate formulated as an aqueous nanoparticle suspension;

ii. For administration by intramuscular injection to a psychiatric patient in need of treatment for schizophrenia, schizoaffective disorder, or schizophreniform disorder;

iii. Wherein the prefilled syringes are adapted for administration in accordance with the following dosing regimen:

    a. A first loading dose of about 150 mg-eq. of paliperidone injected into the deltoid on treatment Day 1;

b. A second loading dose of about 100 mg-eq. of paliperidone injected into the deltoid on treatment Day 8 ± 2 days;

c. Continuous maintenance doses of 75 mg-eq. of paliperidone injected into the deltoid or gluteal monthly ± 7 days thereafter.

[95] The essential elements of claim 2 are the same, except that the patient in need of treatment must have renal impairment, and the claimed dose amounts are about 100 mg-eq., 75 mg-eq., and 50 mg-eq., respectively (*Teva Paliperidone* at paragraph 146).

[96] The essential elements of the claims are conjunctive. The first claim set requires the combination of multiple prefilled syringes of varying dosage amounts adapted for administration in accordance with the claimed dosing schedule and injection sites. The claimed invention is a dosing regimen, not simply dosage forms (*Teva Paliperidone* at paragraphs 147).

[97] Claims 3 through 14 depend from claims 1 and 2, and include further specific formulation limitations. Claims 3 through 14 incorporate the dose amounts, dosing windows, and injection sites from independent claims 1 and 2 (*Teva Paliperidone* at paragraph 128).

[98] Claim 15 further limits any of claims 1 to 14 to administration to a psychiatric patient in need of treatment for schizophrenia only. Claim 16 is similar, but limited to psychiatric patients in need of treatment for schizoaffective disorder only (*Teva Paliperidone* at paragraph 129).

[99] Claims 1 to 16 comprise “product” claims (*Teva Paliperidone* at paragraphs 145 to 147).

[100] Claims 17 to 32 effectively mirror claims 1 to 16, except that they are directed towards "use of a dosage form of paliperidone as paliperidone palmitate" rather than prefilled syringes (*Teva Paliperidone* at paragraph 148).

[101] Claims 17 and 18 claim the same dosing regimen as claims 1 and 2. Claims 19 to 30 include the same formulation limitations as claims 3 to 14. Claims 31 and 32 are identical to claims 15 and 16 except for the claims upon which they depend (*Teva Paliperidone* at paragraph 149).

[102] Where the same terms are used in claims 17 to 32, they have the same meaning as defined above for claims 1 to 16. The only additional claim term in need of construction in this claim set is "use of a dosage form" (*Teva Paliperidone* at paragraph 150).

[103] The POSITA would understand "use of a dosage form" in claims 17 and 18 to mean the use of a syringe containing a depot formulation of paliperidone as paliperidone palmitate to administer the formulation by intramuscular injection according to the dosing and administration schedule in the claims (*Teva Paliperidone* at paragraph 152).

[104] Claims 17 to 32 comprise "use" claims (*Teva Paliperidone* at paragraph 153).

[105] Claims 33 to 48 also mirror claims 1 to 16, except that they are directed towards "use of paliperidone as paliperidone palmitate for the preparation [or manufacture] of a medicament" (*Teva Paliperidone* at paragraph 154).

[106] Claims 33 and 34 claim the same dosing regimen as claims 1 and 2. Claims 35 to 46 include the same formulation limitations as claims 3 to 14. Claims 47 and 48 are identical to claims 15 and 16 except for the claims upon which they depend (*Teva Paliperidone* at paragraph 155).

[107] Where previously used terms are repeated in claims 33 to 48, they have the same meaning as defined above for claims 1 to 16. The only additional claim term in need of construction in this claim set is “preparation [or manufacture] of a medicament” and “medicament form” (*Teva Paliperidone* at paragraph 156).

[108] “Medicament” means a medicine, and is distinguishable from the term “dosage form” as used in claims 33 and 34 in that a medicament does not require a delivery means for the formulation. The “medicament” must be suitable for the depot formulation to be administered intramuscularly. Examples of a “medicament” in this context include vials containing the depot formulation. Prefilled syringes and “dosage forms” as used in the earlier claims fall within the meaning of medicament (*Teva Paliperidone* at paragraphs 157 and 158).

[109] Claims 33 to 48 comprise Swiss-type claims and are “product” claims (*Teva Paliperidone* at paragraph 162 to 163).

[110] Claims 49 to 63 were found to be nearly identical to the earlier claims. In addition, the Court did not require further expert evidence since these claims can be construed by their plain and ordinary meaning (*PMS Paliperidone* at paragraph 85).

[111] Claims 49 to 63 comprise “product” claims (*PMS Paliperidone* at paragraph 85; *Teva Paliperidone* at paragraph 125).

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

[112] The POSITA is a worker of ordinary skill in the art, to which the invention relates, and who possesses the ordinary amount of knowledge incidental to that particular trade (*Consolboard Inc. v. MacMillan Bloedel (Saskatchewan) Ltd.*, [1981] 1 SCR 504 (SCC) at paragraph 523). The POSITA may be a team of persons with different skills (*Teva Canada Limited v. Janssen Inc.*, 2018 FC 754 [*Teva Canada*] at paragraph 66, aff'd 2019 FCA 273).

[113] As stated above, the POSITA is not at issue in this proceeding and the Parties agree that the POSITA consists of a team comprised of a clinician, a pharmaceutical formulator, a pharmacometrician, and a pharmacokineticist (*Teva Paliperidone* at paragraphs 98 to 108).

D. *Common General Knowledge*

[114] Common general knowledge is the knowledge 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 information in the public domain (*Sanofi-Synthelabo Canada Inc. v. Apotex Inc.*, 2008 SCC 61 [*Sanofi*] at paragraph 37; *Eurocopter c. Bell Helicopter Textron Canada Ltée*, 2013 FCA 219 at paragraphs 63 to 65).

[115] At the relevant dates, the POSITA would have had the following common general knowledge (*Teva Paliperidone* at paragraphs 109 to 123):

i. Schizophrenia is a lifelong disease with no cure. The POSITA would have had knowledge of typical and atypical antipsychotics for treating schizophrenia.

ii. Depot formulations are designed for intramuscular injection of a relatively large dose of a long-acting drug. In the case of paliperidone palmitate, hydrolyzation of the palmitate ester provides the active compound paliperidone.

iii. Depot formulations could be oil- or aqueous-based and prefilled syringes had been designed for ease of administration.

iv. Dosing of depot formulations varied from drug to drug.

v. Population pharmacokinetic modeling could be used to assist in designing dosing regimens.

vi. The risk of serious adverse effects was a concern with depot formulations due to their long-acting nature.

vii. A risperidone depot formulation, RISPERDAL CONSTA®, was on the market.

viii. Paliperidone is a metabolite of risperidone.

ix. An extended release oral formulation of paliperidone, INVEGA®, was on the market.

x. Aqueous nanoparticle suspensions of paliperidone palmitate had been developed.

[116] During the trial, the experts provided evidence of the following additional common general knowledge at the relevant time:

i. 9-hydroxyrisperidone is an active and equipotent metabolite of risperidone;

ii. Four milligrams per day of oral risperidone therapy reached median plasma levels of approximately 20 to 65 ng/mL at steady-state;

iii. Risperidone is metabolized extensively in the liver into paliperidone;

iv. Paliperidone is equipotent to risperidone;

v. The pharmacological profile of paliperidone closely resembles that of risperidone;

vi. Paliperidone shares a receptor binding profile similar to risperidone;

vii. Paliperidone has a half-life of about one day;

viii. Paliperidone is eliminated by the kidneys;

ix. RISPERDAL CONSTA®, a long-acting injectable of risperidone, requires dose adjustment for patients with renal impairment;

x. INVEGA®, an extended release oral tablet of paliperidone, require dose adjustment for patients with renal impairment;

xi. Body weight is a covariate on the pharmacokinetics that can have an effect on the efficacy of a drug; and

xii. A loading dose can take the form of a higher initial dose, more frequent dosing, or both.

E. *Obviousness*

[117] As a starting point, the 335 Patent is presumed to be valid (subsection 43(2) of the *Patent Act*). Pharmascience bears the burden of establishing obviousness on a balance of probabilities.

[118] The relevant date for assessing obviousness is the first priority date of the 335 Patent: December 19, 2007.

[119] The four part obviousness framework was laid out by the Supreme Court of Canada in *Sanofi* at paragraph 67:

i. Identify the notional "person skilled in the art" and the relevant common general knowledge of that person;

ii. Identify the inventive concept of the claim in question or if that cannot readily be done, construe it;

iii. 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;

iv. Viewed without any knowledge of the alleged invention as claimed, do those differences constitute steps which would have been obvious to the person skilled in the art or do they require any degree of invention?

[120] In areas of invention where advances are often achieved by experimentation, such as the pharmaceutical industry, an "obvious to try" test might be appropriate (*Sanofi* at paragraph 68). In such situations, the following non-exhaustive factors should be taken into account at the fourth step of the obviousness inquiry (*Sanofi* at paragraphs 69 to 71):

i. 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?

ii. 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?

iii. Is there a motive provided in the prior art to find the solution the patent addresses?

iv. What was the actual course of conduct which culminated in the making of the invention?

[121] This Court has considered the "actual course of conduct" factor as part of the "extent, nature and amount of effort required to achieve the invention" factor (*Teva Canada* at paragraph 85; *Tensar Technologies, Limited v. Enviro-Pro Geosynthetics Ltd.*, 2019 FC 277 at paragraph

157). This approach is not inconsistent with the Supreme Court of Canada's guidance in *Sanofi* that obviousness is largely concerned with how a skilled worker would have acted in light of the prior art, but this is no reason to exclude evidence of the history of the invention (*Sanofi* at paragraph 70).

[122] The Federal Court of Appeal has referred to the actual course of conduct factor as "an elaboration of the second factor" (*Bristol-Myers Squibb Canada Co .v Teva Canada Ltd*, 2017 FCA 76 [*Bristol-Myers Squibb FCA*] at paragraph 44).

[123] The Court must be wary of hindsight bias from expert witnesses. It is not fair to a party claiming to have invented a combination invention to break the combination down into its parts and find that, because each part is known, the combination is therefore obvious (*Bridgeview Manufacturing Inc .v 931409 Alberta Ltd. (Central Alberta Hay Centre)*, 2010 FCA 188 [*Bridgeview*] at paragraph 51). The question to ask is whether the POSITA, in light of the state of the art and their common general knowledge, would have come directly and without difficulty to the solution taught by the patent (*Beloit Canada Ltd v. Valmet Oy*, (1986) 8 CPR (3d) 289 (FCA) at 294).

[124] The obviousness inquiry should be undertaken on a claim-by-claim basis (*Zero Spill Systems (International) Inc. v. Heide*, 2015 FCA 115 at paragraph 85).

[125] As I found previously in *Teva Paliperidone* at paragraphs 172 to 175 in regards to claims 1 to 48, which is now extended to all of the claims of the 335 Patent, the validity of dependent

claims 3 to 16, 19 to 32, 35 to 48, and 51 to 63 rises or falls with the inventiveness of the dosing regimens in independent claims 1, 2, 17, 18, 33, 34, 49, and 50. This is because, considering Janssen's Canadian Patent Nos. 2,309,629 and 2,236, 691 (the "629 Patent" and the "691 Patent", respectively) in light of the common general knowledge, a skilled formulator would have arrived at aqueous depot formulations containing nanoparticles of paliperidone palmitate with an average particle size of 1600 nm to 400 nm, with surfactants, buffering agents, suspending agents, and preservatives in the claimed amounts, without any degree of inventiveness. There has been no evidence or argument in this proceeding to the contrary.

[126] The POSITA and common general knowledge have been described in detail above.

[127] In addition, in *Teva Paliperidone* at paragraphs 176 to 188, I found that the inventive concept is a safe and effective dosing regimen using a depot formulation of paliperidone as paliperidone palmitate, formulated as an aqueous nanosuspension for treatment of schizophrenia patients, designed to reach the therapeutic range of plasma concentrations quickly, and maintain patients within that range. For non-renally impaired patients, the dosing regimen is as detailed in claims 1, 17, 33, and 49:

i. 150 mg-eq. of paliperidone as paliperidone palmitate injected into the deltoid on Day 1;

ii. 100 mg-eq. of paliperidone as paliperidone palmitate injected into the deltoid on Day 8 ± 2 days;

iii. 75 mg-eq. of paliperidone as paliperidone palmitate injected into the deltoid or gluteal monthly ± 7 days thereafter.

[128] For renally impaired patients, the dose amounts are adjusted downwards to loading doses of 100 and 75 mg-eq., and maintenance doses of 50 mg-eq., as detailed in claims 2, 18, 34, and 50.

[129] Pharmascience argues that Janssen's experts, Drs. Chue and Ereshefsky, both improperly expanded the inventive concept. I agree that to the extent they both refer to the claims being in respect of a "standardized" dosing regimen, they overstate the inventive concept. As stated previously in *Teva Peliperidone* at paragraph 184, I found that the claims are not "standardized" and that this concept overstates and contradicts the plain language of the claims.

(1) Differences between the state of the art and the inventive concept

[130] As of December 19, 2007, it was known that pharmacokinetic profiles of depot antipsychotics dictate their dosing. There were a number of first-generation depot antipsychotics on the market (some examples below) and one second-generation antipsychotic:

i. Fluphenazine decanoate: Patients had to be gradually switched from oral to the depot injection only after the patient was stabilized on oral medication. A loading dose could not be used to initiate treatment because of an initial spike during a rapid release phase in the first 24 hours following injection and thus adding a loading dose would cause toxic levels of fluphenazine in the body.

ii. Zuclopenthixol decanoate: Like many of the other depot antipsychotics, this medication was only used for patients stabilized on oral medication using dose conversion from the patient's individual oral dose. Oral supplementation was also used to avoid diminished therapeutic response.

iii. Haloperidol decanoate: While the haloperidol papers, such as those authored by Dr. Ereshefsky, studied loading doses of haloperidol decanoate for "very ill patients", this dosing was individualized based on the patient's prior dose of oral haloperidol. Dr. Chue testified that use of loading doses of haloperidol depot injection was not common clinical practice amongst Canadian physicians.

iv. RISPERDAL CONSTA®: Because essentially no drug releases from the depot for the first three weeks, this formulation was not suitable for use with a loading dose; rather, it required oral supplementation over that period.

[131] While the prior art (Goodman & Gilman's The Pharmacological Basis of Therapeutics, 10th ed. (McGaw-Hill: New York, 2001) did state that generally injections of aqueous solutions into the deltoid muscle result in faster absorption, it would be understood that this does not necessarily apply to depot formulations in oil or suspensions, and in any case, it would not be known whether faster absorption would result in a clinically meaningful and beneficial effect. Pharmascience's expert Dr. Gupta admitted that deltoid injections would not be helpful for certain formulations like RISPERDAL CONSTA®, and further agreed that without an understanding of the drug's pharmacokinetics, it would be possible that deltoid injections might result in a high blood plasma concentration level that could result in adverse effects.

[132] As of December 19, 2007, the prior art disclosed the following information regarding a depot paliperidone palmitate injection:

i. Citrome (2007): This review paper disclosed limited information from clinicaltrials.gov regarding seven planned and ongoing clinical trials for a depot of paliperidone palmitate, but does not disclose results, including no efficacy, safety, or pharmacokinetic data from these trials. It also did not provide any details of the paliperidone palmitate depot formulation used in any of the trials. Pharmascience's experts referred to only two (NCT00210548 and NCT00210717) of the seven studies which are discussed below.

ii. Clinicaltrials.gov NCT00210548: relates to a clinical trial of paliperidone palmitate that looked to investigate fixed doses of 50 mg-eq., 100 mg-eq., or 150 mg-eq. on days 1, 8, 36, and 64. "Fixed doses" in this context means that the same dose was given on each day. This is the only trial investigating the use of a loading dose with paliperidone palmitate. All injections were in the gluteal. No safety, efficacy, or pharmacokinetic data are disclosed.

iii. Clinicaltrials.gov NCT00210717: relates to a clinical trial investigating monthly injections of paliperidone palmitate depot "flexibly" dosed (*i.e.* determined by physicians rather than the amounts being pre-set) with 25-100 mg-eq. doses, all of which are to be injected into the gluteal muscle. No safety, efficacy, or pharmacokinetic data are disclosed.

iv. NCT00101634 was to study doses of 25, 5,0 or 100 mg-eq. versus placebo. No dosing schedule is provided in Citrome and site of injection is not disclosed.

v. NCT00147173 was to study doses of 50, 100 and 150 mg-eq. versus placebo. No dosing schedule is provided in Citrome and site of injection is not disclosed.

vi. NCT00073320 was described in Citrome as an "open-label pharmacokinetic study of injections in the arm or buttock". No dosage strengths or dosing schedule is provided.

vii. For NCT00111189, no doses or dosing schedule is provided, and site of injection is not disclosed.

viii. NCT00119756 looked to investigate "safety and tolerability comparing injection in shoulder vs. buttock muscles". No dosage strengths or dosing schedule is provided in Citrome.

ix. Credit Suisse: This is a transcript of an investor meeting disclosing that Janssen filed a submission to the FDA for a monthly depot of paliperidone palmitate available for deltoid and gluteal injections. Credit Suisse makes several comparisons to RISPERDAL CONSTA® (including differences in frequency of dosing, storage needs, needle sizes, and administration sites), but does not make any comparison to RISPERDAL CONSTA®'s initiation strategy (*i.e.* oral supplementation). Dr. Chue opined that the skilled person would believe that like RISPERDAL CONSTA®, the paliperidone palmitate product does not use loading doses. Dr. Ereshefsky stated that, even if the skilled person considered the possibility that it utilized loading doses, they would have no appreciation for the necessity of these doses to be administered into the deltoid, given that Credit Suisse indicates that injections are interchangeable for both sites.

x. The product label for INVEGA®, an oral paliperidone extended-release tablet, provided some pharmacokinetic information about paliperidone based on that formulation. Dr. Chue opined that the skilled person would not extrapolate this information to a paliperidone palmitate intramuscular depot given the formulation differences. It is necessary to conduct pharmacokinetic studies and clinical trials for safety and efficacy with the paliperidone palmitate depot formulation of interest, which was unknown in the prior art. The prior art included patents and patent applications relating to formulations of paliperidone palmitate, including the 629 Patent, the 691 Patent, and WO 2006/114384.105.

xi. Both INVEGA® and RISPERDAL CONSTA® require lower doses of paliperidone for patients with renal impairment.

[133] In light of the 629 and 691 Patents, the Citrome review article, and applicable data from the clinicaltrials.gov, in *Teva Paliperidone* at paragraphs 190 to 197, I found that the differences between the state of the art and the inventive concept are:

i. A depot antipsychotic dosing regimen designed to quickly and safely reach therapeutic plasma concentrations without the need for oral run in, oral supplementation, or dose titration;

ii. The specified dose amounts of paliperidone palmitate of the claimed regimens;

iii. A loading dose regimen administered into the deltoid muscle;

iv. Maintenance doses administered interchangeably in the deltoid or gluteal muscle;

v. Dosing windows of ± 2 days (second loading dose) and ± 7 days (maintenance doses); and

vi. An adjusted regimen of paliperidone palmitate for patients with renal impairment.

[134] I find that the differences between the state of the art and the inventive concept in this proceeding consistent with those found in *Teva Paliperidone*. The information described in the Credit Suisse transcript is broad and does not disclose details of the claims of the 335 Patent that would modify the analysis of the prior art previously examined.

(2) Do the differences constitute steps that would have been obvious to the POSITA?

[135] While Janssen argues that the evidence in this case is entirely consistent with the findings regarding non-obviousness in *Teva Paliperidone*, Pharmascience argues that there are a number of critical differences in the evidence in this proceeding than that heard in the *Teva Paliperidone* proceeding, including:

i. The POSITA would know the safe and effective plasma concentration range of paliperidone to target from the INVEGA® product and that no further studies were needed; and

ii. The Credit Suisse transcript discloses that Janssen had submitted a new drug application to the FDA, including deltoid and gluteal injections, from which the POSITA would understand that such a product was safe and effective.

[136] Viewed without any knowledge of the invention claimed in the 335 Patent, the differences between the state of the art and the inventive concept constitute steps would not have been obvious to the skilled person. The evidence in this case is consistent with the findings regarding non-obviousness in *Teva Paliperidone*.

[137] The state of the art did not set out safety, efficacy, pharmacokinetic, or pharmacodynamics. In order to determine a suitable dosing regimen for paliperidone palmitate long-acting depot injection, at the very least pharmacokinetic information and results from clinical trials both with paliperidone palmitate would be required. As was shown above in the invention story, the skilled person would first have needed to run clinical studies to determine the pharmacokinetic profile of paliperidone injection as this information is crucial in dosing regimen design. As admitted by Pharmascience's expert Dr. Gupta, even if the skilled person chose to investigate a loading dose regimen, studies would be required to determine what loading dose regimen was required to rapidly achieve therapeutic plasma concentrations; and, in any case the prior art did not disclose any safety, efficacy, or pharmacokinetic data for a paliperidone palmitate depot formulation.

[138] It appears that Dr. Gupta's analysis was driven by hindsight. Pharmascience's argument breaks down the dosing regimen into its parts and asserts that each part is well known and, thus, the combination is obvious. This argument ignores several key differences between the state of the art and the regimens claimed in the 335 Patent, including the lack of disclosure regarding formulations of paliperidone palmitate used in the clinical trials listed in Citrome and the NCT documents, the dosing windows of paliperidone palmitate, and a loading dose regimen utilizing

injection into the deltoid; and the fact that no prior antipsychotic depot injection was approved for injection into the deltoid muscle and that loading doses of antipsychotic depot formulations were not commonly used in clinical practice.

[139] The claims are inventive:

i. The dose amount for each injection: the prior art did not disclose a dosing regimen with doses of 150 mg-eq. followed by 100 mg-eq. followed by 75 mg-eq. for paliperidone palmitate. The art disclosed trials with fixed dose amounts whereby each dose was the same amount and one flexible dose study. None of the art pointed to three different pre-set dose amounts used in a specific sequence and specific injection sites to rapidly attain and maintain therapeutic plasma concentrations. Arriving at these dose amounts for each dose was inventive.

ii. Loading doses: while NCT548128 had a Day 1, 8, 36, 64 regimen for paliperidone palmitate, which would be understood as a loading strategy, all doses in that study were fixed (meaning patients received the same dose on each day). The prior art did not disclose two loading doses whereby the amount for each dose was specified regardless of a patient's prior treatment or any patient specific factor (other than renal impairment). The only other long-acting antipsychotic disclosed in the art that had explored use of loading doses in clinical studies was haloperidol decanoate, which determined the loading dose based on the amount of oral haloperidol the patient had been receiving, rather than one regimen designed to safely and effectively achieve and maintain therapeutic plasma concentrations. All other drugs in the prior art utilized either oral supplementation or titration,

including RISPERDAL CONSTA®, which is directly contrasted against Janssen's proposed paliperidone palmitate product in Credit Suisse, without any mention of the proposed product being improved because it used loading doses and did not require oral supplementation. Furthermore, the prior art did not disclose a loading dose regimen whereby a loading dose of 150 mg-eq. followed by a second loading dose of 100 mg-eq. is administered on days 1 and 8. The loading dose regimen of the 335 Patent claims was arrived at following significant clinical investigations as well as population pharmacokinetic analyses. This aspect of the claims was inventive.

iii. Deltoid injections: No long-acting depot antipsychotic in the prior art was approved for injections into the deltoid muscle, and no clinical trial of paliperidone palmitate in the prior art even investigated loading doses into the deltoid muscle, let alone a study that required two loading doses of unequal amounts of paliperidone palmitate to be administered into the deltoid muscle. The prior art disclosed gluteal injections to be the preferred injection site. Although Credit Suisse discloses that both deltoid and gluteal will be available for the planned monthly product (which at that stage might or might not have been approved), this does not provide any information as to requiring loading doses to be in the deltoid (particularly since Credit Suisse does not even mention loading doses and only refers to monthly administration). Without pharmacokinetic information, the skilled person would not know whether administration of a depot antipsychotic drug into the deltoid would result in a clinical difference. Further, without pharmacokinetic data, the skilled person would not know if

administration of a depot antipsychotic into the deltoid leads to “toxic” levels of drug in the body. Requiring administration of the first two doses into the deltoid muscle as part of a loading dose regimen was inventive.

iv. The dosing schedule: the prior art disclosed that at least two dosing regimens were being investigated with paliperidone palmitate depot, including dosing once a month, dosing the same dose on Days 1, 8, 36, and 64 into the gluteal muscle, as well as several investigations with unspecified dosing regimens. Without clinical trial results, the skilled person would not know which, if any, dosing schedule was preferred. The skilled person would know that clinical trials fail and without results would have nothing to guide them. Indeed, although not known to the skilled person, the NCT548 trial (the only trial in the prior art that disclosed a loading dose regimen with paliperidone palmitate) failed, proving that phase III trials do indeed fail. Based on Credit Suisse, the skilled person would also be led to assume a monthly injection was to be used without a loading regimen. A dosing schedule whereby pre-set doses of paliperidone in three different amounts were administered on Days 1, 8, and monthly thereafter was inventive.

v. The dosing windows: the prior art did not disclose or mention any dosing windows, including dosing windows for the second loading dose or for the monthly maintenance dose. This dosing windows element was inventive.

vi. Dosing for renally impaired patients: the prior art did not disclose or mention dosing of paliperidone palmitate in patients with renal impairment. Without knowing the dosing regimen for patients without renal impairment, the skilled

person could not apply an adjustment. Further, there was no information in the prior art as to the degree of adjustment required for patient with renal impairment being administered paliperidone palmitate; in fact, Dr. Gupta stated that it could be true that no dosing adjustment for the loading doses would need to be made. The dosing regimen for patients with renal impairment was inventive. However, the common general knowledge, as stated above, does include that paliperidone is eliminated by the kidneys, and both RISPERDOL CONSTA® and INVEGA® both required adjustments for renally impaired patients.

vii. Dosing regimen as a whole: The evidence shows that the specific combination of the dosing regimen elements as claimed in the 335 Patent was not obvious.

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

[140] In a pharmaceutical invention such as this, where the advance in the art was made as a result of experimentation, this question is best answered by an application of the "obvious to try" test outlined in *Sanofi* at paragraphs 69 to71.

[141] The obvious to try analysis must be approached cautiously; it is not a panacea for alleged infringers (*Sanofi* at paragraph 64). The factors to be considered are those laid out by the Supreme Court of Canada in *Sanofi*.

[142] In order to satisfy the test 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" (*Sanofi* at paragraph 66; see also *Pfizer Canada Inc. v. Apotex Inc.*, 2009 FCA 8 [*Pfizer*]; *Hospira Healthcare Corporation v. Kennedy Trust for Rheumatology Research*, 2020 FCA 30 [*Hospira FCA*] at paragraph 88). A high degree of motivation to find a solution to a problem does not transform any discovered solution into an obvious solution (*Pfizer* at paragraph 44). Evidence of tests being required indicates the invention was not self-evident (*Allergan Inc. v. Canada (Minister of Health)*, 2014 FC 567 at paragraphs 34-35, aff'd 2015 FCA 137).

[143] Considering the factors of the *Sanofi* obvious to try test, the evidence shows that the invention of the 335 Patent was not more or less self-evident to the skilled person, given that there were numerous potential paths that the skilled person could have pursued without ever arriving at the dosing regimens claimed in the 335 Patent. There was not a finite number of identified predictable solutions. Indeed Dr. Gupta does not propose a finite number of identified solutions, let alone any predictable solutions. A significant amount of skill, effort, and non-routine work, as well as inventiveness would be required to arrive at the subject matter claimed in the 335 patent, particularly given the lack of any human pharmacokinetic, safety, or efficacy results for paliperidone palmitate.

[144] While Pharmascience argues that the target therapeutic plasma concentration would have been known from the prior art, the questions of whether a depot formulation of paliperidone palmitate administered intramuscularly using the claimed dosing regimens would have reached and maintained the therapeutic plasma concentration safely and effectively was not known and required significant skill and effort as set out above in the invention story.

[145] The evidence of Dr. Gupta is that further experimentation was required, including determining the pharmacokinetic profile of paliperidone palmitate depot. As explained by Janssen's experts, further clinical trials also would be needed to investigate different dosing regimens. As Drs. Ereshefsky and Chue explained, clinical trials are not routine, often fail, and require a great amount of arduous effort. Moreover, Dr. Gupta's own testimony reveals the result of his proposed further studies was not predictable to him. When suggesting a loading dose would be investigated he stated "If the loading dose determined to be required…exceeds 150 mg…", and agreed that he is saying "if" because "you don't know" what loading dose would be determined to be required to rapidly attain therapeutic plasma concentrations based on the prior art, you have to do studies to figure that out.

[146] Similarly, the Citrome (2007) paper concludes that "The depot intramuscular preparation holds greater promise ***if*** it can be demonstrated that it can be administered less frequently than risperidone intramuscular microspheres and that there is little lag time prior to the development of adequate blood level (emphasis added)" it is because even to the author it was unknown whether paliperidone palmitate depot could be administered less frequently without little lag time prior reaching adequate blood levels.

[147] The evidence of an expert must not be conclusory and must provide supporting analysis (*Bridgeview* at paragraph 53). As stated above, it appears that Dr. Gupta approached the analysis with hindsight (*Bristol-Myers Squibb Canada Co. v. Teva Canada Ltd.*, 2016 FC 580 at paragraph 165, aff'd *Bristol-Myers Squibb FCA*; *GlaxoSmithKline Inc. v. Pharmascience Inc.*, 2011 FC 239 at paragraph 70).

[148] Dr. Gupta offers an opinion from the perspective of a formulator/pharmacokineticist. On cross-examination, Dr. Gupta admitted he does not have experience performing pharmacokinetic trials on humans and he did not do any analysis and does not offer any opinion on the clinical aspects of the 335 Patent.

[149] Dr. Gupta did not provide evidence on how a skilled person could have arrived at the specific dosing regimen taught by the 335 Patent in light of the prior art. He also did not address the claimed dosing windows.

> (3) 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?

[150] The POSITA need not be capable of conducting the same experiments that the inventors did to reach the claimed invention (*Hospira FCA* at paragraph 94). As stated above, the fourth factor, the actual course of conduct, is inherently tied to the second factor, and sheds light on the amount of effort required to reach the claimed invention (*Sanofi* at para 71; *Bristol-Myers Squibb FCA* at paragraph 44).

[151] Although "obviousness is largely concerned with how a skilled worker would have acted in the light of the prior art" an "important factor may arise from considering the actual course of conduct which culminated in the making of the invention" (*Sanofi* at paragraph 70).

[152] Further, "Where those involved … were highly skilled in the particular technology involved, the evidence may suggest that the skilled person would have done a lot worse and

would not likely have managed to find the invention. It would not have been obvious to [them] to try the course that led to the invention" (S*anofi* at para 71; see also *Bayer Inc. v. Cobalt Pharmaceuticals Co.*, 2016 FC 1031 at paragraph 138).

[153] Dr. Ereshefsky's opinion is that the inventors' course of conduct was complex, time and resource consuming, and non-routine. The inventors encountered unexpected set-backs in phase III of development; had to revise the dosing regimens several times, including because they encountered unsuccessful phase III studies; and as a result of their "complex and non-routine" work were able to develop a regimen which quickly and safely achieves therapeutic concentrations of paliperidone in patients regardless of BMI. The work of the inventors, including use of population pharmacokinetic modelling, resulted in a dosing regimen which contains several completely novel and inventive features, and ensures a consistent plasma concentration profile without the need for conversion, oral supplementation, oral run-in, or titration, something which was previously not seen with any other depot antipsychotic drug.

[154] As stated above, Dr. Gupta's opinion that only routine work was needed is weakened by his lack of experience in conducting pharmacokinetic of clinical trials in humans – the experts and witnesses with first hand knowledge of the events spoke to the issues encountered, and skill and effort needed to overcome them to arrive at the invention.

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

[155] As found in *Teva Paliperidone* at paragraph 219, the experts agreed that there would have been a general motivation to develop a depot formulation of paliperidone, but not necessarily a specific motivation to develop the dosing regimens contained in the 335 Patent. The POSITA would have known of the benefits of depot formulations over oral treatments for patients with compliance issues. However, at the time, depot formulations were indicated for maintenance treatment, not for patients experiencing acute symptoms, and known dosing regimens required oral run in, oral supplementation, or dose titration.

(5) Conclusion on obviousness

[156] Having considered all of the expert evidence and the prior art, I am not satisfied that Pharmascience has met its burden. While the added formulation elements in the dependent claims may not be inventive, each of the independent claims of the 335 Patent incorporates one of the dosing regimens as essential elements, which results in all of the claims being non-obvious.

[157] Pharmascience primarily relies on Dr. Gupta's expert opinion evidence that the claims are obvious. However, Dr. Gupta suffered some credibility issues in failing to agree to or admit to simple propositions, and never conducted or designed a clinical trial or pharmacokinetic trial in humans. As stated above, Dr. Gupta's evidence is conclusory and driven by hindsight. He broke the dosing regimen down into its component parts and concluded that the claimed combination was therefore obvious (*Bridgeview* at paragraph 51).

[158] Recognizing that the obvious to try factors laid out in *Sanofi* are not exhaustive, after reviewing the above factors, I am satisfied that the difference between the state of the art and the inventive concept of the 335 Patent claims would not have been obvious to the POSITA.

[159] I find that the combination of the claimed dosing regimen elements in the claims of the 335 Patent is inventive, and the claims of the 335 Patent are not obvious.

F. *Method of Medical Treatment*

[160] Section 2 of the *Patent Act* defines patentable subject matter. An "invention" is "any new and useful art, process, machine, manufacture or composition of matter, or any new and useful improvement in any art, process, machine, manufacture or composition of matter." The prohibition on methods of medical treatment is rooted in the Supreme Court of Canada's decision in *Tennessee Eastman Co. et al. v. Commissioner of Patents* (1972), [1974] SCR 111.

[161] As I have previously discussed, there are inconsistencies in Canadian law on what constitutes a method of medical treatment which has been highlighted by judges of this Court and the Federal Court of Appeal (*Teva Paliperidone* at paragraph 143). However, the common starting point is to examine the language and substance of the claims: "what do the claims say?" (*Bayer Inc. v. Cobalt Pharmaceuticals Company*, 2013 FC 1061 [*Bayer*] at paragraph 162).

[162] Pharmascience argues that, in accordance with *Teva Paliperidone*, the selection of the maintenance doss – from within the range of 25 to 150 mg-eq. as available in the product monographs for INVEGA SUSTENNA® and the proposed pms-PALIPERIDONE

PALMITATE – depends upon individual characteristics. The experts agreed that a particular maintenance dose may not work for every patient and the physician, alongside the patient, would need to determine the most safe and efficacious maintenance dose depending on various factors, including adverse side effects, other medications, comorbidities, etc. As such, the choice of a maintenance dose within the range in accordance with the product monographs would require skill and judgment on the part of the prescriber (*Teva Paliperidone* at paragraph 290; *PMS Paliperidone* at paragraph 137).

[163] However, there appears to be no question in the case law that claims to a vendible product are patentable as not being methods of medical treatment (see for example, *Apotex Inc. v. Wellcome Foundation Ltd.*, 79 CPR (3d) 193 (FC) at paragraph 74, aff'd 10 CPR (4th) 66 (FCA) at paragraph 74, aff'd 2002 SCC 77 at paragraph 50; *Merck & Co Inc. v. Pharmascience Inc.*, 2010 FC 510 at paragraph 110 [*Merck 2010*]; *Novartis Pharmaceuticals Canada Inc. v. Cobalt Pharmaceuticals Co.*, 2013 FC 985 [*Novartis*] at paragraph 78, aff'd 2014 FCA at paragraph 3; *Biogen Canada Inc. v. Taro Pharmaceutical Inc.*, 2020 FC 621 [*Biogen*] at paragraph 22). As stated above, claims 1 to 16, and 33 to 63 are "product" claims (*Teva Paliperidone* at paragraphs 145 to 147 and 162 to 163; *PMS Paliperidone* at paragraph 85) and are not "methods" of medical treatment. Therefore, the method of medical treatment analysis is only relevant in respect of claims 17 to 32, which are "use" claims (*Teva Paliperidone* at paragraph 153; *Merck 2010* at paragraph 111).

[164] For use claims, the analysis is on the essential claim elements to determine whether professional skill and judgment is required to practice the invention as claimed. A claim for

"use" of a medicine to treat a patient is not an unpatentable method of medical treatment if it includes a specific dosage amount and/or specific administration interval. With respect to dosing elements, the law has evolved such that claims restricted to particular dosages and specific administration schedules have been found to be patentable subject matter, where the amounts and timing are fixed (see for example, *Merck & Co Inc. v. Apotex Inc*., 2005 FC 755 at paragraph 136; *Merck 2010* at paragraph 111; *AbbVie Biotechnology Ltd. v. Canada (Attorney General)*, 2014 FC 1251 at paragraph 121; *Bayer* at paragraph 162; *Hospira FCA* at paragraphs 52 to 53; *Biogen* at paragraphs 211 and 213; *Hoffmann-La Roche Limited v. Sandoz Canada Inc*., 2021 FC 384 at paragraphs 197 and 202 (distinguished from the claims of the 335 Patent in *Teva Paliperidone* at paragraph 103)), whereas claims to dosages or schedules with ranges within which the physician must exercise skill and judgment have been found to not be a vendible product and thus not patentable (*Janssen Inc. v. Mylan Pharmaceuticals ULC*, 2010 FC 1123 at paragraphs 52 to 53; *Bayer* at paragraph 162; *Novartis* at paragraphs 98 to 99).

[165] While this dichotomy, between specific dosages and administration intervals contrasted with ranges of dosages and schedules, has led to a series of cases wherein the former has been held to be patentable, vendible products and the latter, at least in some cases, as being unpatentable as requiring skill and judgment amounting to methods of medical treatment, seems to have a questionable underpinning in resulting judgments based on this dichotomy, nevertheless that is where we are under the current state of decisions up to and including decisions in the Federal Court of Appeal.

[166] As stated by Justice Locke in *Hospira FCA* at paragraph 52:

> This state of the jurisprudence has a tempting simplicity. However, it is not clear to me that the decisions of the Supreme Court of Canada that form the basis of the principle that methods of medical treatment are not patentable justify a distinction between a fixed dosage (or interval of administration) and a range of dosages (or intervals). It would seem that a medical professional will be constrained in their exercise of skill in either case. Also, a drug is arguably no less a vendible product simply because its dosage or interval of administration is not fixed.

[167] As Pharmascience's expert Dr. Jeffries agreed, claims 17-32 do not prevent physicians from practicing in a manner they had previously "because they weren't doing anything before" the 335 Patent with paliperidone palmitate to treat schizophrenia.

[168] In addition, claims 17 to 32 do not require professional skill and judgment; there are no choices in respect of possible ranges for the dosage amounts, which are fixed at loading doses of 150 mg-eq. on Day 1, 100 mg-eq. on Day 8, and 75 mg-eq. thereafter as the maintenance dose for non-renally impaired patients, and loading doses of 150 mg-eq. on Day 1, 100 mg-eq. on Day 8, and 75 mg-eq thereafter as the maintenance dose for non-renally impaired patients, and loading doses of 100 mg-eq. on Day 1, 75 mg-eq. on Day 8, and 50 mg-eq. thereafter as the maintenance dose for renally impaired patients.

[169] The use claims provide for two possible dosing regimens, one for non-renally impaired patients and another for renally impaired patients. Once a physician chooses to use the products for the purpose claimed, each of the claims teaches fixed dose amounts, fixed intervals, and fixed injection sites.

[170] While there are elements where there are choices (dosing windows around the Day 8 and monthly doses, and injection sites for the maintenance dose), those choices do not have clinical implications. The experts explained the dosing windows are incorporated into the regimen to allow flexibility in order to avoid a missed dose without significant clinical difference, and the maintenance dose injection site is clinically interchangeable. Therefore, no skill and judgment is required that would interfere with or restrict a physician's skill or judgment in deciding to prescribe the dosing regiment within the claimed invention.

[171] The claims are a guide for the treatment of schizophrenia, providing specific dosing regimens expected to produce a plasma concentration of paliperidone within the therapeutic range necessary for safe and effective treatment of patients. A physician can choose to implement a claimed specific dosing regimen or not; however, skill and judgment are not required to implement the claimed dosing regimens. To the extent a physician chooses a maintenance dose other than 75 mg-eq. (as is contained in the product monograph and which much cross-examination and testimony were focused), or decides to stop treatment with paliperidone palmitate and switch therapies, they would no longer be practicing the claimed invention. Thus, the claimed subject matter does not require the exercise of skill and judgment and is not a method of medical treatment.

[172] I find that the 335 Patent discloses patentable subject matter.

V. Conclusion

[173] In conclusion, Pharmascience has not established that the claims of the 335 Patent are invalid on the basis of either obviousness or lack of patentable subject matter (*i.e.* as a method of medical treatment).

[174] As previously found in the motion for summary trial on the sole issue of infringement in Court file No. T-1441-20, the proposed pms-PALIPERIDONE PALMITATE product made, constructed, used, or sold as set out in ANDS No. 244641 will infringe the claims of the 335 Patent.

[175] As stated above, the Notice of Allegation in accordance with ANDS No. 251767 does not contest infringement of the claims of the 335 Patent by the making, constructing, using, or selling of a proposed pms-PALIPERIDONE PALMITATE as set out in ANDS No. 251767.

VI. Costs

[176] The Plaintiffs submit that the Court should consider a reasonable costs award to the successful party on the validity phase of both actions before the Court, (excluding costs for the previous summary trial), and should be calculated according to one of three scenarios:

i. a lump sum award of $1.5 million, inclusive of all legal fees, disbursements and taxes; or

ii. a lump sum award of 25% of all legal fees plus all disbursements and taxes; and any dispute about reasonableness of fees and disbursements to be determined by an assessment officer; or

iii. costs to be assessed at the top of column IV of Tariff B of the *Federal Court Rules*;

iv. post-judgment interest of 3.5%.

[177] The Defendant submits that if the Plaintiffs are successful, they should be awarded costs:

i. in T-1441-20, in accordance with the middle of column III of Tariff B;

ii. in T-558-22, costs should be limited to preparation of pleadings and assessed in accordance with the middle of column III of Tariff B, in a separate order;

iii. fees of Dr. Chue should be reduced by 33% given that he provided unhelpful and unnecessary evidence dealing with obviousness and on issues (decided in *Janssen Inc. v Tera Canada Ltd.*, 2020 FC 593) (*Teva Paliperidone*), and

iv. fees of Dr. Ereshefsky should be reduced by 50%, given he provided unhelpful and unnecessary evidence on obviousness and issues in the *Teva Paliperidone* matter and he used recycled evidence on the same patent in the *Teva Paliperidone* matter;

v. legal fees and costs should be awarded to Pharmascience with respect to the failure of the Plaintiffs to call Dr. Gobburu, on a solicitor-client basis;

vi. no costs or fees should be awarded for the fact affidavits of the inventors, Dr. Gopal, Dr. Vermeulen and Dr. Samtani, given their evidence is substantially the same as was used in the *Teva Paliperidone* matter;

[178] Having carefully considered the parties' written representations and relevant case law, and the nature of the evidence tendered by the witnesses at trial, as well as the conduct of the witnesses during the trial, I find as follows:

The Plaintiffs are hereby awarded a lump sum of 25% of all reasonable legal fees plus 100% of all reasonable disbursements and taxes, and any dispute about reasonableness of those fees and disbursements shall be determined by an assessment officer if no agreement is reached within 45 days from the issuance of this decision, with the following limitations to be accounted for:

i. The fees of Dr. Ereshefsky and Dr. Chue are reduced by 25%. As stated in my reasons above, there was inconsistent evidence given by each of these witnesses having regard to their previous testimony in related proceedings and at times their testimony was not forthcoming when it should have been.

ii. No fees are awarded for Dr. Gobburu, and costs are awarded to Pharmascience for all reasonable costs thrown away given the last minute failure to call him as a witness at the trial;

iii. Post-judgment interest shall be calculated at 2.5%;

JUDGMENT in T-1441-20 & T-558-22

THIS COURT'S JUDGMENT is that:

1. The claims of the 335 Patent are not obvious, and are valid.

2. The claims of the 335 Patent are not methods of medical treatment, are patentable subject matter, and are valid.

3. The making, constructing, using, or selling of pms-PALIPERIDONE PALMITATE by Pharmascience in accordance with ANDS Nos. 244641 and 251767 will infringe the claims of the 335 Patent.

4. An injunction is granted until the expiry of the 335 Patent on December 17, 2028, restraining Pharmascience, as well as its subsidiary and affiliated companies, officers, directors, employees, agents, licensees, successors, assigns, and any others over whom it exercises lawful authority, from:
    a. Making, constructing, using or selling pms-PALIPERIDONE PALMITATE in Canada in accordance with ANDS Nos. 244641 and 251767;
    b. Offering for sale, marketing or having pms-PALIPERIDONE PALMITATE marketed in Canada in accordance with ANDS No. 244641 and 251767; and
    c. Importing, exporting, distributing or having pms-PALIPERIDONE PALMITATE distributed in Canada in accordance with ANDS Nos. 244641 and 251767.

5. Janssen is awarded 25% of reasonable legal fees and 100% of reasonable disbursements, exclusive of any motions for which costs have been fixed including the motion for summary trial in Court file no. T-1441-20, with the following limitations:

    a) the fees of Dr. Ereshefsky and Dr. Chue are reduced by 25%;

    b) No fees are awarded for Dr. Gobburu, and costs are awarded to Pharmascience for all reasonable costs thrown away given the last minute failure to call him as a witness at the trial.

6. Within 45 days of receiving this decision, the Parties will endeavour to agree on a reasonable costs quantum in accordance with the foregoing parameters, failing which the costs shall be assessed by an assessment officer in accordance with these reasons and judgment.

"Michael D. Manson"
Judge

FEDERAL COURT

SOLICITORS OF RECORD

DOCKET:	T-1441-20 & T-558-22
STYLE OF CAUSE:	JANSSEN INC. AND JANSSEN PHARMACEUTICA N.V. v. PHARMASCIENCE INC.
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