Federal Court  Cour fédérale

Date: 20200505

Docket: T-353-18

Citation: 2020 FC 593

Ottawa, Ontario, May 5, 2020

PRESENT: The Honourable Mr. Justice Manson

BETWEEN:

JANSSEN INC.

Plaintiff

and

JANSSEN PHARMACEUTICA N.V.

Plaintiff
(Defendant by Counterclaim)

and

TEVA CANADA LIMITED

Defendant
(Plaintiff by Counterclaim)

PUBLIC JUDGMENT AND REASONS

I. Introduction

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

Janssen Inc, a corporation headquartered in Toronto, and Janssen Pharmaceutica NV, a corporation headquartered in Belgium [collectively Janssen].

[2] Janssen Inc is a "first person" as defined in the *Regulations*, and Janssen Pharmaceutica NV 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]. Janssen Inc is authorized by Janssen Pharmaceutica NV to sell INVEGA SUSTENNA® (paliperidone palmitate) in Canada.

[3] The Defendant, Teva Canada Ltd [Teva] is a generic pharmaceutical company headquartered in Toronto. Teva filed an Abbreviated New Drug Submission [ANDS] with Health Canada, seeking approval to sell its own paliperidone palmitate product in Canada. On January 9, 2018, Teva served Janssen with a Notice of Allegation pursuant to the *Regulations*, prompting the commencement of this action.

II. Background

A. *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 1970’s, 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 antipsychotics block D2 receptors in the brain, and work well against positive symptoms of schizophrenia. However, they are also associated with high incidence of severe adverse side effects called extrapyramidal symptoms, typically involving motor control symptoms such as muscle spasms, muscle rigidity, restlessness, and jerky movements.

[10] Atypical antipsychotics entered the market in the 1990s, and act on both dopamine and serotonin receptors. Atypical antipsychotics have a far lower propensity to cause extrapyramidal symptoms.

[11] Because 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 not 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 a prolonged dose of the drug.

B. *The 335 Patent*

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

[14] 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. It contains 63 claims, and Janssen alleges infringement of claims 1 to 48 [the Asserted Claims].

[15] The invention relates to dosing regimens for long acting injectable paliperidone palmitate formulations for treatment of schizophrenia. The goal of the invention was to develop 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.

[16] In order to rapidly achieve therapeutic blood plasma concentrations, the patent teaches a "loading dose" regimen comprising doses of paliperidone palmitate administered on day 1 and day 8 in the deltoid muscle, followed by a "maintenance dose" regimen comprising doses of paliperidone palmitate administered monthly thereafter, in either the deltoid or gluteal muscle.

[17] The dosing regimen incorporates "dosing windows" of ± 2 days for the second loading dose, and ± 7 days for the monthly maintenance doses. The dosing windows build flexibility into the regimen without impacting therapeutic effect.

[18] The Asserted Claims of the 335 Patent break down into three 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; and

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.

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

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;

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

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

C. *The Invention Story*

[21] Janssen started working on a long acting injectable paliperidone formulation in the early 1990s, forming a global research team to support its development. Around 2003, this team was labelled the Paliperidone Palmitate Compound Development Team [PP CDT].

[22] 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.

[23] Dr. An Vermeulen, a pharmacometrician at Janssen, was actively involved in developing the dosage regimen for paliperidone palmitate. Initial multi-dose studies conducted at Janssen indicated that with once monthly injections, patients would only reach steady-state plasma concentrations of paliperidone after 4-5 months. In 1999, Dr. Vermeulen designed BEL-7, a phase 1 study comparing two different loading dose regimens: (1) administering a double dose on day 1 with monthly dosing thereafter; and (2) administering the same dose on days 1 and 8 with monthly dosing thereafter. All doses were administered in the gluteal. BEL-7 showed that the second loading dose regimen with fixed doses on days 1 and 8, and monthly thereafter, resulted in steady state plasma concentrations within the first month.

[24] Following phase 1 clinical trials, Dr. Vermeulen developed a population pharmacokinetic [popPK] model to assist in making informed dosing decisions and support dosing regimen selections. Based on the results of BEL-7 and Dr. Vermeulen's modeling, Janssen moved forward with a phase 2 study—SCH-201—in 2003, testing fixed doses of 50 and 100 mg-eq on days 1, 8, and monthly thereafter. Based on the success of SCH-201, Janssen designed two phase 3 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. These studies were conducted from December 2004 to March 2006, and June 2005 to June 2006, respectively.

[25] 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 3 clinical trials. At this time, PSY-3003 and PSY-3004 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 3 studies and propose improvements to the dosing regimen.

[26] To assist in revising the dosing regimen, Dr. Vermeulen developed a new popPK model using clinical data from over 1200 patients. She used this model to evaluate different dosing regimens by simulating the plasma concentrations of a virtual but representative patient population.

[27] 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.

[28] In 2006, Dr. Vermuelen 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 popPK model for Janssen's long acting injectable paliperidone palmitate formulation.

[29] Dr. Samtani used Dr. Vermeulen's model as a starting point, and built a new model using data from over 1400 patients, comprising 15,000 samples from phase 1, 2, and 3 studies. His model took into account a wide range of covariates and paliperidone palmitate's complex

absorption and elimination process. It took approximately six months to build and externally validate the model, and once it was complete, he ran simulations to guide optimization of the paliperidone palmitate dosing regimen.

[30] 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, 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 3 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 oral doses of extended release paliperidone.

[31] While Janssen did not receive the PSY-3007 results until after the 353 Patent claim date, Dr. Samtani had developed this regimen using his popPK model, and confirmed the safety and efficacy of the regimen in part using the PSY-3007 results.

[32] Dr. Samtani also used his model to develop recommended dosing windows, that is, flexible tolerance intervals for the timing of the second loading dose and subsequent maintenance dose injections. 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 impacting safety and efficacy. Based on modeling and clinical data, Dr. Samtani also determined the appropriate downward dose adjustments for renally impaired patients.

III. Issues

[33] At the outset of trial, three primary issues remained: infringement, and invalidity on the bases of obviousness and unpatentable subject matter. During the course of the trial, Teva withdrew its plea of unpatentable subject matter, leaving only obviousness and infringement in dispute.

[34] The remaining issues are:

A. Are the Asserted Claims of the 335 Patent invalid for obviousness?

B. Will Teva directly infringe or induce infringement of the 335 Patent if it comes to market with its paliperidone palmitate product?

[35] For the reasons that follow, I find that:

A. The Asserted Claims are not obvious, and are valid.

B. Teva will directly infringe claims 1 to 16 and 33 to 48 of the 335 Patent if it comes to market with its paliperidone palmitate product in accordance with its ANDS. Claims 17 to 32 will not be directly infringed, and Teva will not induce infringement of any of the Asserted Claims.

IV. Fact Witnesses

A. *Janssen's Fact Witnesses*

(1) An Vermeulen, PhD

[36] Dr. Vermeulen is a named co-inventor of the 335 Patent. She is currently a Senior Scientific Director and Fellow in Janssen's Quantitative Sciences Consulting Group.

[37] Dr. Vermeulen joined Janssen Pharmaceutica NV in 1992 as a scientist, and joined the Pharmacometrics Department as a Pharmacometrician in 2001. In this role, she was responsible for developing pharmacokinetic models, popPK models, and population pharmacodynamic models. Dr. Vermeulen used models to guide decision making, design clinical trials, and support dose regimen selection and adaptation.

[38] Dr. Vermeulen gave evidence on her work in the development of the formulation and dosing regimens for Janssen's paliperidone palmitate injectable.

(2) Mahesh Samtani, PhD

[39] Dr. Samtani is a named co-inventor of the 335 Patent. He is currently a senior director at Janssen Research & Development, involved in all stages of drug development. He joined the PP CDT in February 2007 as a pharmacometrician.

[40] Dr. Samtani gave evidence on his work in the development of the paliperidone palmitate dosing regimen, however his credibility was called into question. He was obstructionist on cross-examination, and did not give straightforward answers to many simple questions. Dr. Samtani was clearly very impressed with his own modeling work.

(3) Srihari Gopal, MD

[41] Dr. Gopal is a named co-inventor of the 335 Patent. He is currently Senior Director (Head of Development, Psychiatry) at Janssen Research & Development. He is also the current team leader of the PP CDT, having initially joined the team as a clinician in 2006.

[42] Dr. Gopal gave evidence about his role in the development of the paliperidone palmitate one month long acting injectable formulation.

[43] Dr. Gopal took several unreasonable positions on cross-examination. He was presented with a 2014 Janssen publication where he is listed as an author, describing a study where the dosing regimen used was 150 mg-eq on day 1 in the deltoid, 100 mg-eq on day 8 in the deltoid, followed by a monthly maintenance doses in the range of 25 to 150 mg-eq in either the deltoid or gluteal muscle. Dr. Gopal stated that reference to a range of maintenance doses was likely due to a “cut and paste” error, and as of the publication date of the paper a maintenance dose range was “definitely not the company position.”

[44] Despite the clear description of the maintenance dose range, and acknowledging that he and his co-authors would have reviewed the paper, Dr. Gopal maintained that Janssen did not recommend any maintenance dose other than 75 mg-eq at that time.

[45] Similarly, counsel for Teva produced a 2009 paper co-authored by Dr. Gopal for submission to Health Canada and the United States Food and Drug Administration that states "[g]ood clinical practice is to individualize treatment based upon clinical symptoms. Individualization of the dose of paliperidone palmitate can begin as early as Day 36, the time corresponding to the third injection." Despite acknowledging that he was familiar with the document, and the document had been submitted to the regulatory authorities, Dr. Gopal testified that this statement is not correct.

[46] Further, Dr. Gopal stated during examination for discovery that any of the maintenance doses work, depending on patient needs and the prescribing physician's choice. Janssen decided to recommend a single dose to provide guidance to the physician as to which dose to start with, and 75 mg-eq was selected based on the average maintenance dose for oral paliperidone, as well as the common maintenance dose of paliperidone palmitate used in the flexible dose studies. The read-ins from Dr. Gopal's discovery paint a different picture of Janssen's company position on the maintenance dose than the one he gave on cross-examination.

[47] Dr. Gopal's inconsistent positions on cross-examination as compared to statements made during discovery and in papers he co-authored weakened his credibility.

B. *Teva's Fact Witnesses*

(1) David Boughner

[48] Mr. Boughner is the Senior Director of Commercial Management for Teva. He provided evidence that Teva does not market to doctors, and with the exception of product monographs [PMs], does not market its generic products generally.

V. Expert Witnesses

A. *Janssen's Expert Witnesses*

(1) Ofer Agid, MD

[49] Dr. Agid is a medical doctor with specialized training in psychiatry. He is a psychiatrist and clinician scientist in the Schizophrenia Program at the Centre for Addiction and Mental Health [CAMH] in Toronto, with a particular focus on diagnosis, treatment, and management of psychotic disorders, including schizophrenia.

[50] Dr. Agid obtained his medical degree at the Hebrew University in Jerusalem, Israel in 1992. He completed a psychiatry residency with the Israeli Psychiatric Association in 1999, and joined CAMH in 2001 as a post-doctoral fellow in clinical research.

[51] In addition to his clinical roles at CAMH, Dr. Agid previously served as a committee member on the CAMH Pharmacy and Therapeutics Committee, which is responsible for

creating, reviewing, and implementing policies and procedures in respect of drug products at the hospital. Dr. Agid also carries out schizophrenia research in association with CAMH and the University of Toronto, and is an Associate Professor of Psychiatry at the University of Toronto.

[52] Dr. Agid was qualified as an expert in the diagnosis, treatment, and management of psychotic disorders, including schizophrenia, schizoaffective disorder, schizophreniform disorder, and treatment-resistant schizophrenia, and the nature and clinical use of antipsychotic drugs, including INVEGA SUSTENNA, for the treatment of psychotic disorders, including schizophrenia, schizoaffective disorder, schizophreniform disorder, and treatment-resistant schizophrenia. While he opined on the prescribing practices of physicians in Canada with respect to antipsychotic drugs for these indications, his evidence on this issue is given only limited weight as being for the most part hearsay.

[53] He gave evidence on issues of claim construction, infringement, and obviousness.

[54] On cross-examination, Dr. Agid suffered from two credibility issues. First, he seemed to take contrary positions between his expert report and cross-examination. He repeatedly took the position that the claims allow for treatment using only a single maintenance dose. This position is inconsistent with his report, where he states that treatment must be continuous due to the untreatable nature of schizophrenia.

[55] He was steadfast in his interpretation that the skilled clinician could understand the claims to include only a single maintenance dose, despite the plain claim language that the

maintenance doses are adapted for intramuscular administration according to a continuous schedule having a monthly ± 7 days dosing interval.

[56] Second, Dr. Agid maintained that the dosing regimen described in the 335 Patent was the "optimized and standardized" regimen. When pressed by counsel for Teva, Dr. Agid pointed to claim 1 of the patent as support for this position. However, the examples and preferred embodiments in the patent describe numerous different dosing regimens. Dr. Agid could not point to anything in the disclosure that supported his position that the claimed dosing regimen is an "optimized and standardized" dosing regimen.

[57] In addition to these two credibility issues, Dr. Agid admitted that physicians would focus on the "Dosage and Administration" section of a PM, including both Janssen and Teva's paliperidone palmitate PMs. This admission tends to undermine his position that practicing clinicians would interpret the Teva PM as recommending a maintenance dose of 75 mg-eq based on the entirety of the document.

(2) Barrett E. Rabinow, PhD

[58] Dr. Rabinow is a consultant in the field of pharmaceutical sciences. He obtained his PhD in physical-organic chemistry from the University of Chicago in 1974, and completed postdoctoral work in electrochemistry at the University of Chicago, and clinical chemistry at the National Institute of Health in Chicago.

[59] From 1977 to 2016, Dr. Rabinow worked as a scientist for Baxter Healthcare Corporation, in the areas of parenteral products and sterile fluids, including troubleshooting manufacturing problems and developing nanosuspension drug formulation platforms.

[60] Dr. Rabinow was qualified as an expert in pharmaceutical formulation development and manufacturing, including with respect to liquid formulations for parenteral administration and the preparation and use of suspensions and nanosuspensions in formulations and dosage forms, including injectable dosage forms. This expertise includes excipient selection, and the analysis and characterization of physical and chemical properties of nanosuspension pharmaceutical formulations, including pH, particle size distribution, viscosity, and isotonicity.

[61] Dr. Rabinow opined on formulation aspects of the 335 Patent, and infringement by Teva.

(3) Richard Jones

[62] Mr. Jones is a pharmacist, and is currently the Regional Director of Pharmacy Services at the Vancouver Island Health Authority.

[63] He was qualified as an expert in drug formulary management, including the process and considerations involved in listing a drug product on the hospital drug formulary; and pharmacy practice and medication management in a hospital setting, including prescribing methods, drug dispensing practices and pharmacy clinical practise processes. His evidence was focused on the use of generic PMs in pharmacy practice, hospital formulary management, and pharmacy drug dispensing practices.

[64] Mr. Jones was a credible witness. At times, he appears to have overstated the involvement of the pharmacist in the prescribing process, which is a task within the mandate of the clinician, but overall his testimony was credible and helpful in establishing the role of the pharmacist in the prescription process, as well as the availability of specific drugs within a hospital formulary.

(4) Robert Bies, PharmD, PhD

[65] Dr. Bies is an Associate Professor at the School of Pharmacy and Pharmaceutical Sciences at the State University of New York at Buffalo, an Adjunct Associate Professor at the Department of Pharmacology and Therapeutics at the Roswell Park Cancer Institute, and an Adjunct Associate Professor of Clinical Pharmacology at the Indiana University School of Medicine. His research area focuses on pharmacokinetic and pharmacodynamic mathematical modeling and simulation techniques.

[66] Dr. Bies obtained his PharmD from the University of Texas in 1994, and received his PhD in pharmacology from Georgetown University in 1998. He completed postdoctoral studies at the Center for Drug Development Sciences at Georgetown University between 1998 and 2000. From 2006 to 2016, Dr. Bies served as a research scientist at the CAMH, providing pharmacometric modeling support to investigators studying antipsychotics.

[67] Dr. Bies was qualified as an expert in pharmacometrics, including:

- Developing, selecting, and utilizing pharmacokinetic, pharmacodynamic, and population pharmacokinetic and

pharmacodynamic mathematical models of drugs, including antipsychotic drugs;

- Application of pharmacometric approaches to psychiatry; and

- Analyzing simulations from pharmacokinetic, pharmacodynamic, and population pharmacokinetic and pharmacodynamic mathematical modeling, including for therapeutic response modeling of antipsychotic drugs.

[68] Dr. Bies testified to the issue of obviousness and the course of conduct of the inventors, and he was a credible witness. At times he seemed somewhat evasive on cross-examination, however this appears to have arisen from his desire to be precise in answering questions.

(5) Larry Ereshefsky, PharmD

[69] 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.

[70] Dr. Ereshefsky obtained his PharmD from the University of Southern California in 1976 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 from 1977-2003, teaching courses in psychiatric therapeutics and clinical pharmacology.

[71] 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.

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

- Clinical pharmacology, particularly clinical pharmacology of antipsychotic drugs;
- Evaluating the pharmacokinetics, pharmacodynamics, bioequivalence, drug-drug interactions, and pharmacogenetics of antipsychotic drugs, including depot antipsychotics;
- Clinical use of antipsychotic drugs, including designing treatment plans for patients;
- Clinical trial design and implementation, particularly for schizophrenia drugs;
- Translational psychopharmacology, including evaluation of preclinical data and models to predict pharmacokinetic and pharmacodynamic parameters in humans;
- Evaluation of toxicology and safety signals.

[73] Dr. Ereshefsky testified to the issue of obviousness and the course of conduct of the inventors. He was a credible witness.

B. *Teva's Expert Witnesses*

(1) Richard F. Bergstrom, PhD

[74] Dr. Bergstrom is an Adjunct Professor of Medicine at the Indiana University School of Medicine in the Clinical Pharmacology Division of the Department of Medicine. He obtained his PhD in Pharmaceutical Chemistry (Pharmacokinetics) from the University of Michigan in 1980.

[75] Dr. Bergstrom worked at Eli Lilly and Company between 1973 and 2008, primarily as a pharmacokineticist. In this role, he was responsible for many projects involving the design and evaluation of pharmaceutical dosage forms and formulations, including depot formulations for intramuscular injection. His role in these projects was to use his pharmacokinetic expertise to assist in designing dosage forms, formulations, and dosing regimens.

[76] Dr. Bergstrom was qualified as an expert on issues relating to bioavailability, pharmacokinetics, and pharmacodynamics, including in the development of pharmaceutical formulations, including depot formulations.

[77] Dr. Bergstrom opined on the issue of obviousness of the dosing regimen aspects of the claims, and overall he was a credible witness. However, at times he was evasive on questions relating to obviousness, and took unreasonable positions with respect to how the skilled pharmacokineticist would understand some of the clinical trial information cited in his own report. In his report, he suggested that phase 3 clinical trials were indicative that development of a dosing regimen was in its final stages; however, on cross-examination he suggested that the

clinicaltrials.gov website does not always accurately list phase 1, 2, and 3 trials, and downplayed the importance of phase 3 clinical trials.

[78] Despite his view that the development of the dosing regimen would have been routine, Dr. Bergstrom acknowledged on cross-examination that depot formulation development is a long and difficult process because the doses are given infrequently, and it takes a long time to assess this type of trial. Further, phase 3 trials are not always successful, so ongoing phase 3 trials do not necessarily indicate that drug development is nearing completion

(2) Adil Virani, PharmD

[79] Dr. Virani is a Clinical Associate Professor at the University of British Columbia's Faculty of Pharmaceutical Sciences, and a Manager of Pharmacy Services for Lower Mainland Pharmacy Services. He has been a licensed pharmacist since 1992, and trains medical and pharmacy students on topics relating to mental health, substance abuse, and pain management.

[80] Dr. Virani obtained his PharmD from the University of British Columbia in 1997. He has extensive clinical experience in evidence-based practices, specifically psychopharmacology in pediatric and adult disorders. He has experience treating patients with various psychiatric conditions with antipsychotic medications, including INVEGA SUSTENNA.

[81] Dr. Virani was qualified as an expert in psychopharmacology, the listing of drugs on hospital formularies, and hospital pharmacy management. His evidence was focused on the use of PMs in pharmacy practice.

[82] Dr. Virani's evidence was helpful to the Court. He answered questions clearly on cross-examination, and was not evasive. He did not advocate for any position, but gave evidence as to how he understands and uses PMs, and the role of pharmacists in the prescription and verification process.

[83] During cross-examination, Dr. Virani stated that in a collaborative healthcare setting such as a hospital, pharmacists may review *and change* a physician's prescription if the pharmacist is of the opinion that the dose is not appropriate for the patient in question. This aligns closely with Mr. Jones' testimony that a pharmacist may actively question a physician on their choice of dose; a point that counsel for Teva attempted to minimize in cross-examination.

[84] That said, Dr. Virani agreed that pharmacists do not prescribe medicine in the traditional sense, and a hospital pharmacist could not write a prescription to be filled outside the hospital.

(3) James Simm, MD

[85] Dr. Simm is the Medical Director at the PACT Logan Winnipeg Regional Health Authority. His responsibilities in this role include directing a community outreach team for patients with severe, persistent mental illness, including schizophrenia. He obtained his medical degree from the University of Manitoba in 1995.

[86] In past positions, Dr. Simm has directed outpatient clinics for patients with schizophrenia, attended to patients admitted to the hospital with schizophrenia, and directed an inpatient unit caring for patients with both addictions and mental illness. Dr. Simm is also an

Associate Professor at the University of Manitoba. His responsibilities in this role include teaching clinical skills to medical students and supervising psychiatry residents who are training in addiction psychiatry.

[87] Dr. Simm gave evidence on the use of PMs in clinical practice and his paliperidone palmitate prescribing practices. He was a credible witness.

(4) Glen Kwon, PhD

[88] Dr. Kwon is a Professor at the School of Pharmacy at the University of Wisconsin-Madison and an adjunct Professor in the Faculty of Pharmacy and Pharmaceutical Sciences at the University of Alberta. His responsibilities include teaching pharmacy students about the use and manufacture of injectable drug depots.

[89] Dr. Kwon obtained his PhD from the University of Utah in 1991, and completed postdoctoral studies in bioengineering at Tokyo Women's Medical College. His current research focuses on polymeric nanotechnology for drug delivery, including studying drug solubilization, controlled drug release, and drug targeting for injectables.

[90] Dr. Kwon was qualified as an expert in the development of pharmaceutical formulations, including injectable formulations. He was a credible witness, acknowledging that his expertise was limited to the formulation aspects of the 335 Patent. He opined that the formulation aspects of the Asserted Claims were obvious at the relevant date.

(5) Suzanne Allain, MD

[91] Dr. Allain is a staff psychiatrist at St. Joseph's Hospital and Thunder Bay Regional Hospital in Thunder Bay. Her clinical work is largely focused on inpatient treatment of patients with schizophrenia and related diseases.

[92] Dr. Allain obtained her MD from the University of Toronto in 1988, and completed a residency in psychiatry at the University of British Columbia in 1993. She is an Associate Professor at the Northern Ontario School of Medicine, an Adjunct Professor in the Department of Psychiatry at Western University, and an Assistant Professor in the Department of Psychiatry at the University of Toronto.

[93] Dr. Allain was qualified as a psychiatrist who specializes in the treatment of schizophrenia, schizoaffective disorder, and schizophreniform disorder, particularly in patients with chronic or treatment resistant disease. She gave evidence on the use of PMs in clinical practice, and her paliperidone palmitate prescribing practices.

[94] Dr. Allain was a credible witness. She stood steadfast in her opinion that the claimed maintenance dose must be administered on a "continuous" monthly schedule.

VI. Claim Construction

[95] Claim construction is a matter of law for the judge (*Whirlpool Corp v Camco Inc*, 2000 SCC 67 at para 61 [*Whirpool*]). 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 paras 25, 35-36; *Excalibre Oil Tools Ltd v Advantage Products Inc*, 2016 FC 1279 at para 119).

[96] The principles of claim construction in Canadian patent law were laid out by the Supreme Court of Canada in *Whirlpool* and *Free World Trust* (*Whirlpool*, above, at paras 49-55; *Free World Trust v Électro Santé Inc*, 2000 SCC 66 at paras 44-54 [*Free World Trust*]). These principles are as follows:

> i. Claims are to be read in an informed and purposive way, with a mind willing to understand and viewed through the eyes of the skilled reader, as of the date of publication, having regard to the common general knowledge;
>
> ii. Adherence to the language of the claims allows them to be read in the manner in which the inventor is presumed to have intended, and in a way that is sympathetic to accomplishing the inventor's purpose, which promotes both fairness and predictability;
>
> iii. The whole of the specification should be considered, in order to ascertain the nature of the invention, and the construction of the claims must be neither benevolent nor harsh, but instead should be reasonable and fair to both the patentee and the public; and
>
> iv. On a purposive construction, the claim language will show that some elements are essential while others are non-essential. The identification of claim elements as essential or non-essential is made on the basis of the common knowledge of the worker skilled in the art to which the patent relates as of the patent publication date.

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

A. *Person of Ordinary Skill in the Art [POSITA]*

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

[99] The parties' experts agreed that the POSITA team includes a clinician with experience treating schizophrenia, and a pharmaceutical formulator. In addition to these team members, Janssen's experts opined that the POSITA includes a pharmacometrician and a clinical pharmacologist. Teva's experts opined that the POSITA additionally includes a pharmacokineticist, but not a pharmacometrician or clinical pharmacologist.

[100] Janssen submits that because Figures 1-3 and Example 7 in the 335 Patent relate to popPK modeling, the POSITA should include a pharmacometrician with expertise in developing this type of model. As explained by Dr. Bies, a pharmacokineticist would not necessarily have expertise in developing popPK models.

[101] I agree that the 335 Patent disclosure includes figures and results based on popPK modeling, however the invention is not directed towards developing popPK models. The POSITA is a team "sufficiently versed in the art to which the patent relates to enable them on a technical level to appreciate the nature and description of the invention" (*Whirlpool* at para 53).

Accordingly, the POSITA need only understand the figures and features of paliperidone's pharmacokinetics identified using the models, a skill set the pharmacokineticist would possess. Expertise *developing* popPK models is not required to understand the 335 Patent.

[102] That said, the parties ultimately appear to agree on this point. Teva submits that the POSITA has skills related to "pharmacokinetics and pharmacodynamics, including modeling" and Teva further relies on the testimony of Dr. Bies—Janssen's expert pharmacometrician—for evidence that the skilled person would have known how to build a popPK model. The Court is satisfied that the POSITA would have had sufficient expertise to both develop and interpret the results of popPK models.

[103] The knowledge and skills of Janssen's "clinical pharmacologist" and Teva's "pharmacokineticist" largely overlap. As acknowledged by Dr. Ereshefsky on cross-examination, a POSITA team comprised of a clinician, formulator, and pharmacokineticist would possess the relevant skills and knowledge of the clinical pharmacologist as defined by him.

[104] Having considered the expert testimony on the composite POSITA, I find that the POSITA team is comprised of a clinician, a pharmaceutical formulator, a pharmacometrician, and a pharmacokineticist.

[105] The clinician POSITA would have a medical degree and at least three to five years of experience treating patients with psychotic disorders, including schizophrenia and its related disorders. The clinician would understand the diagnosis, pathophysiology, treatment, and

management of these disorders, and would be aware of antipsychotics available to treat these disorders, including their mechanisms of action, indications, side effects, and dosing.

[106] The formulator POSITA would have at least an MSc in pharmaceutical sciences, chemistry, or a related field, and three to five years of industry experience in industrial pharmaceutical formulation development. The formulator POSITA would have specific experience developing depot formulations.

[107] The pharmacometrician would have a background in pharmacy or a PharmD degree, and expertise in pharmacokinetic and pharmacodynamic modeling, including popPK modeling.

[108] The pharmacokineticist POSITA would have an advanced degree specializing in pharmacokinetics or pharmacology, and would have experience working in a drug development setting. The pharmacokineticist POSITA would have experience developing and evaluating drug dosing regimens with depot formulations, seeking to maximize drug effect while minimizing the risk of adverse effects. They would have an understanding of pharmacokinetic and pharmacodynamic modeling, including popPK modeling.

B. *Common General Knowledge*

[109] 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 (*Apotex Inc v Sanofi-Synthelabo Canada Inc*, 2008 SCC 61 at

para 37 [*Sanofi*]; *Bell Helicopter Textron Canada Limitée v Eurocopter, société par actions simplifiée*, 2013 FCA 219 at paras 63-65).

[110] Drs. Ereshefsky and Bies opined that there is no difference between the POSITA's common general knowledge on the claim date of December 19, 2007, and the patent publication date of June 19, 2009. Similarly, Dr. Agid provided essentially the same description of the common general knowledge in his claim construction and obviousness opinions. Teva did not highlight any changes in the common general knowledge between December 19, 2007 and June 19, 2009, so the following summary of the POSITA's common general knowledge will apply to both the claim construction and obviousness analyses.

[111] The POSITA's common general knowledge includes the technical background detailed at the beginning of these reasons. In addition to this general background on schizophrenia and its treatment, the POSITA would have known that depot antipsychotics were typically synthesized by adding long chain fatty acids to the active drug and dissolving the resulting compound in an oil. Depot formulations could also be aqueous based, and aqueous based depot formulations have advantages over oil-based formulations. Prefilled syringes had been developed for ease of depot formulation administration.

[112] Known advantages of depot formulations include:

- Improved patient adherence;
- More constant plasma concentrations than with oral medication;
- They are not subject to first-pass elimination;

- They can be administered on a weekly to monthly basis;
- Doses and administration intervals can be individualized based on the patient; and
- Rapid stabilization on depot antipsychotics can reduce the length of stay for acute inpatients, decrease recidivism rates, and decrease total cost of care.

[113] As of the relevant date, several typical antipsychotics were available as oil-based depot formulations. Only one atypical antipsychotic depot formulation—Risperdal Consta (risperidone)—had come to market. Risperdal Consta was formulated as an aqueous suspension of microspheres containing risperidone, and was administered via intramuscular injection every two weeks.

[114] The POSITA would have been aware that the atypical antipsychotic olanzapine pamoate, was being investigated as a depot formulation. Patients receiving olanzapine pamoate injections were at risk of developing post-injection delirium sedation syndrome, which resembled an olanzapine overdose. The common understanding at the time was this was a result of "dose dumping," or premature release of a high dose of olanzapine from the depot.

[115] The therapeutic range of a given drug is the range of drug concentration in the body that provides a therapeutic effect with minimal toxic effects. A dosing regimen is the administration schedule for the drug to bring drug levels into the therapeutic range. The POSITA would have been aware that the pharmacokinetic profile of a depot antipsychotic impacted the appropriate dosing regimen. Dosing of depot antipsychotics varied between different drugs, and even between different formulations of the same drug.

[116] Dosing regimens typically specify the following parameters:

- Dose approach (e.g. variable, fixed dosing);
- Route of administration (e.g. oral, intravenous, intramuscular);
- Dosing interval (e.g. daily, weekly, monthly, etc);
- Dose amount (e.g. mg of compound administered with each dose); and
- Adjustments for special populations (e.g. hepatic or renal impairment).

[117] Many drugs require repeated administration to achieve and maintain therapeutic effect. The POSITA would have known that a loading dose is a single dose or series of doses given at the beginning of therapy with the goal of reaching a target drug concentration in the body quickly. A loading dose may take the form of a single, higher dose amount, and/or more frequent dosing of the maintenance dose amount at the initiation of treatment. Known disadvantages of using loading doses were the risk of exposing the patient to potentially toxic concentrations of the drug, and the length of time it would take for the drug concentration to fall from a toxic level, for drugs with long half lives.

[118] The POSITA would have been aware that models could be used to assist in dosing regimen design. PopPK modeling relies on concentration-time data from multiple individuals, or uses pooled pharmacokinetic and pharmacodynamic data from more than one study. The POSITA would have known the major considerations for developing, validating, and interpreting the results of a popPK model. Predictive popPK models can be used to predict dose-concentration-effect relationships and aid in designing clinical trials.

[119] The typical approach to dosing depot antipsychotics as of 2007 was to switch patients from oral medications to depot medications. First, patients would be stabilized on the oral form of the medication. Once symptoms were controlled, a suitable depot dose would be determined using a conversion factor, and the patient would switch to depot therapy. Many depot formulations required supplementation with oral medications where desired plasma concentrations were not achieved sufficiently quickly following depot injection. For example, Risperdal Consta required oral supplementation for three weeks after the initial depot injection.

[120] Many depot antipsychotics used dose titration to ensure a gradual rise in plasma concentration. One fear of using depot antipsychotics was severe adverse effects, as once the depot is injected, the drug stays in the patient for an extended period of time. To check for adverse effects, patients would often receive a tolerability dose to ensure they had no immediate adverse reactions.

[121] The POSITA would have known that paliperidone is an active metabolite of risperidone. As of the relevant date, paliperidone was available as an extended release tablet for oral administration in the range of 3 to 12 mg daily. Paliperidone is excreted through the kidneys, and hence paliperidone is eliminated more slowly in renally impaired patients.

[122] When paliperidone is administered as a depot injection of paliperidone palmitate, the paliperidone palmitate is hydrolyzed in the body to give paliperidone—the active compound—and palmitic acid. Release of paliperidone from the depot is the limiting factor in the time it takes

for the drug concentration to reach steady state. The POSITA would have been aware that aqueous nanoparticle suspensions of paliperidone palmitate had been developed.

[123] To summarize, at the relevant dates the POSITA would have had the following common general knowledge:

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. PopPK 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 was on the market.

viii. Paliperidone is a metabolite of risperidone.

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

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

C. *Claim Terms Needing Construction*

(1) Claims 1 to 16: Prefilled syringes

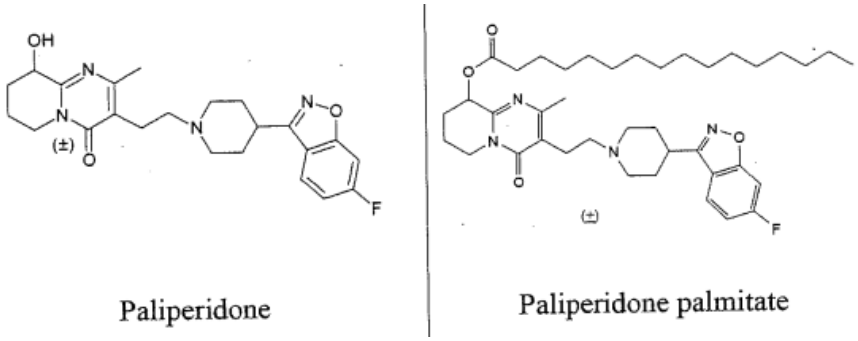
[124] Claims 1 to 16 cover prefilled syringes containing a depot formulation of paliperidone as paliperidone palmitate. Claim 1 reads as follows:

> 1. Prefilled syringes containing a depot formulation of paliperidone as paliperidone palmitate formulated as an aqueous nanoparticle suspension for administration by intramuscular injection to a psychiatric patient in need of treatment for schizophrenia, schizoaffective disorder, or schizophreniform disorder, wherein the prefilled syringes comprise:
>
> a) a first prefilled syringe containing a first loading dose of the depot formulation comprising about 150 mg-eq. of paliperidone as paliperidone palmitate, wherein the first prefilled syringe is adapted for intramuscular administration into a deltoid muscle of the psychiatric patient on a first day of treatment;
>
> b) a second prefilled syringe containing a second loading dose of the depot formulation comprising about 100 mg-eq. of paliperidone as paliperidone palmitate, wherein the second prefilled syringe is adapted for intramuscular administration into a deltoid muscle of the psychiatric patient one week ± 2 days after the first loading dose; and
>
> c) a prefilled syringe containing a maintenance dose of the depot formulation comprising about 75 mg-eq. of paliperidone as paliperidone palmitate, wherein the prefilled syringe is adapted for intramuscular administration into a deltoid or a gluteal muscle of the psychiatric patient according to a continuous schedule having a monthly ± 7 days dosing interval after the second loading dose.

[125] This is one of those touchstone cases where the Court generally does not need expert aid in construing the terms of the Asserted Claims. There is nothing in the 335 Patent specification to indicate that the inventors sought to act as their own lexicographers, and the claim terms should be given their plain, ordinary meaning.

[126] The parties largely agree on the construction of claim 1. The following claim elements are not in dispute, and would be understood by the POSITA as defined below:

> **Prefilled syringes** are syringes that come from the manufacturer already filled with the drug formulation.
>
> **Depot formulation** is a type of sustained release dosage form that forms a reservoir in the area of the body where it is administered, allowing for release and subsequent absorption of the active drug ingredient over an extended period of time.
>
> **Paliperidone as paliperidone palmitate** means the palmitate ester of paliperidone, the active drug ingredient. The structures of paliperidone and paliperidone palmitate are pictured below.



Paliperidone | Paliperidone palmitate

> **Aqueous nanoparticle suspension** is a type of formulation of solid paliperidone palmitate nanoparticles suspended in a water-based medium.
>
> **For administration by intramuscular injection** means that the formulation is to be injected into muscle tissue.
>
> **A psychiatric patient in need of treatment for schizophrenia, schizoaffective disorder, or schizophreniform disorder** means a patient with any of these psychotic disorders, as defined in the technical background, who is in need of drug therapy to treat their symptoms.
>
> **Loading dose** is a dose used to quickly bring the blood plasma concentration of the drug into the desired therapeutic range.
>
> **Maintenance dose** is a dose used to maintain the steady state plasma concentration of the drug within the therapeutic range.
>
> **About (150/100/75) mg-eq.** means the amount of paliperidone palmitate required to provide the stated dose of paliperidone. One mg-eq of paliperidone palmitate is the amount required to give 1

> mg of the active drug paliperidone. "About" means some variability in the amount is allowable.
>
> **Adapted for intramuscular injection** means the drug delivery system is suitable for injecting the formulation into a muscle.
>
> **Deltoid muscles** are the muscles located at the uppermost part of the patient's arms.
>
> **Gluteal muscle** is the group of muscles making up the patient's buttocks.
>
> **A first day of treatment** means the day on which treatment is initiated, that is, the day on which the first loading dose is administered to the psychiatric patient.
>
> **One week ± 2 days after the first loading dose** means 5 to 9 days after the first loading dose. If the first loading dose is administered on day 1, the second loading dose is to be administered on day 6, 7, 8, 9, or 10.
>
> **Monthly ± 7 days dosing interval after the second loading dose** means 28 days, ± 7 days, after the second loading dose. Maintenance doses are to be administered 21 to 35 days after the previous dose.

[127] Claim 2 covers prefilled syringes for administration to renally impaired psychiatric patients. The experts agreed that a renally impaired psychiatric patient is a psychiatric patient with impaired kidney function. Claim 2 specifies the first, second, and maintenance doses as about 100 mg-eq, 75 mg-eq, and 50 mg-eq of paliperidone as paliperidone palmitate respectively.

[128] Claims 3 through 14 depend from claims 1 and 2, and include further specific formulation limitations. Dr. Rabinow construed each formulation element in these claims. Dr. Kwon did not construe the claim elements, but rather opined on whether the formulation elements were taught in the prior art. In any event, the construction of the formulation elements

does not appear to be in dispute, and claims 3 through 14 incorporate the dose amounts, dosing windows, and injection sites from independent claims 1 and 2.

[129] 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. The meaning of these disorders is not in dispute, and is described in the technical background.

[130] The only real controversy between the parties is whether the phrase "continuous schedule" requires the ongoing administration of maintenance doses, or requires a single maintenance dose only. Related to this dispute is how the POSITA would understand the term "comprises" as used in claims 1 and 2. Both parties couched their arguments on this point in terms of essentiality.

[131] Janssen's position, as supported by the opinions of Drs. Agid and Ereshefsky is that only one maintenance dose is essential. Janssen submits that further maintenance doses may be administered beyond the first maintenance dose, but the claims do not require further maintenance doses.

[132] Teva's position, as supported by the opinions of Drs. Allain and Simm, is that the maintenance dose referred to in claims 1 and 2 is intended to be administered on an ongoing basis and would not be understood by the POSITA to be limited to a single administration.

[133] Teva submits that this construction is supported by the evidence of Dr. Samtani—one of the inventors of the 335 Patent—who stated on cross-examination that the inventors' intention was to establish a continuous maintenance dosing schedule, not merely three injections.

[134] Evidence from an inventor put forward at trial constitutes extrinsic evidence which should not be considered by the Court when construing the claims (*Free World Trust*, above, at para 66; *Eurocopter v Bell Helicopter Textron Canada Limitée*, 2012 FC 113 at para 321, aff'd 2013 FCA 219). Notwithstanding Teva's position that Dr. Samtani's evidence supports its proposed claim construction, the Court should not resort to his evidence on this point.

[135] Dr. Agid opined that the POSITA would understand the term "comprises" to mean "including but not limited to." Therefore, claims 1 and 2 cover three prefilled syringes, but could also include additional prefilled syringes. Because the claims are directed towards a continuous treatment schedule for disorders that have no cure, the POSITA would understand the claims to contemplate ongoing monthly maintenance doses. However, Dr. Agid stated that the POSITA would know that the continuous schedule could end after one maintenance dose or any number of maintenance doses.

[136] Dr. Agid appeared to be advocating for Janssen's construction position, and I do not accept that the POSITA, based on a purposive reading of the claims having regard to the common general knowledge at the relevant time, would follow this line of reasoning.

[137] Janssen submits that only three prefilled syringes are essential to claim 1, and no reasonable alternative of the term "continuous schedule" exists. If ongoing continuous monthly maintenance doses are essential, the claims would cover an indefinite, uncertain number of doses. On cross-examination Dr. Bergstrom stated that he did not know how many maintenance doses were included in the maintenance dose regimen.

[138] On its face, the maintenance dose regimen defined in claims 1(c) and 2(c) refers to "a prefilled syringe containing a maintenance dose" (emphasis added). However, the words "continuous schedule having a monthly ± 7 days dosing interval" must be given purposive meaning. The POSITA's knowledge of the nature of schizophrenia as a chronic disease requiring continuous treatment supports a finding that the maintenance dose regimen is not limited to a single prefilled syringe. Further, the words "monthly" and "continuous" are used repeatedly throughout the disclosure. The clinical trials and modeling figures described in the disclosure all reference at least two monthly maintenance doses.

[139] To suggest that "continuous schedule" be interpreted as a single dose asks the Court to impart a construction of these words that is inconsistent with their plain, ordinary meaning. The Court will not do so. As acknowledged by Dr. Agid on cross-examination, if a physician administered only one maintenance dose, treatment of that patient would stop. As stated in the disclosure, one goal of once monthly injections is to increase treatment adherence over daily oral treatment regimens. Administration of only one maintenance dose is not consistent with improved treatment adherence.

[140] While the plain meaning of the claim language is sufficient to dispense with Janssen's position on claim construction, Teva further submits that Janssen's position is inconsistent with representations it made before the Patent Office during prosecution of the 335 Patent, thereby engaging section 53.1 of the *Patent Act*, RSC 1985, c P-4. This provision permits written communications between the patentee and the Patent Office made during the prosecution of a Canadian patent application to be admitted into evidence to rebut representations made by the patentee in the action as to the construction of a claim in the patent (*Canmar Foods Ltd v TA Foods Ltd*, 2019 FC 1233 at para 60).

[141] In a June 26, 2015 letter to the Commissioner of Patents, Janssen represented that claim 1 as amended and ultimately issued, when purposively construed, provides:

> - a vendible product: prefilled syringes containing a depot formulation;
> - containing fixed doses:150 mg-eq, 100 mg-eq, 75 mg-eq;
> - for administration on a fixed dosing schedule that does not involve physician skill or judgement: <u>day 1, one week ± 2 days, continuous schedule having a monthly ± 7 days dosing interval</u>;
> - via intramuscular injection into a specified site of administration, the choice of which does not involve physician skill and judgement.
>
> [emphasis added]

[142] The construction advanced by Janssen during prosecution is consistent with the plain meaning of the claim language, and inconsistent with Janssen's position at trial that only one maintenance dose is essential to claim 1. I find that section 53.1 of the *Patent Act* is engaged, and the written communication between Janssen and the Commissioner of Patents dated June 26,

2015 is admissible. This evidence supports Teva's position that the maintenance doses referred to in claim 1 are intended to be administered on an ongoing basis.

[143] As is evident from the above excerpt from the June 26, 2015 letter, Janssen amended the claims to overcome a patentable subject matter objection on the basis that the previously claimed dosing regimens covered a method of medical treatment. While Teva ultimately withdrew its plea of unpatentable subject matter such that methods of medical treatment are no longer directly at issue in this matter, the inconsistency in Canadian law on what constitutes a method of medical treatment has clearly played a part in the prosecution and litigation of the 335 Patent. As highlighted by judges of this Court and the Federal Court of Appeal, consideration—and clarification—of the prohibition on methods of medical treatment is warranted, although that clarification is not at play in this case (*Cobalt Pharmaceuticals Company v Bayer Inc*, 2015 FCA 116 at para 101; *Hospira Healthcare Corporation v Kennedy Trust for Rheumatology Research*, 2018 FC 259 at para 141 [*Hospira*]; *Hospira Healthcare Corporation v Kennedy Trust for Rheumatology Research*, 2020 FCA 30 at para 53 [*Hospira FCA*]).

[144] A purposive construction of a maintenance dose on a "continuous schedule" can only result in a finding that it means maintenance dosing on an ongoing basis, not one dose.

[145] To summarize, the essential elements of claim 1 are:

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

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

- Wherein the prefilled syringes are adapted for administration in accordance with the following dosing regimen:
    - A first loading dose of about 150 mg-eq of paliperidone injected into the deltoid on treatment day 1;
    - A second loading dose of about 100 mg-eq of paliperidone injected into the deltoid on treatment day 8 ± 2 days;
    - Continuous maintenance doses of 75 mg-eq of paliperidone injected into the deltoid or gluteal monthly ± 7 days thereafter.

[146] 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.

[147] It is important to note that 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.

(2) Claims 17 to 32: Use of a dosage form

[148] 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.

[149] 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.

[150] 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."

[151] Drs. Agid, Ereshefsky, and Bergstrom essentially agreed that the POSITA would understand "use of a dosage form" to mean the paliperidone palmitate formulation and a delivery system to administer the formulation to the patient. The dosage form must contain both the formulation and means to administer it to the patient. The dosage form must be suitable for administration by intramuscular injection, which would mean a syringe body and a needle.

[152] Therefore 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.

[153] The parties agree that this claim set comprises use claims, and Teva will not directly infringe these claims.

(3) Claims 33 to 48: Use of paliperidone as paliperidone palmitate for the preparation of a medicament

[154] 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."

[155] 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.

[156] 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."

[157] Dr. Bergstrom states that the term "medicament" would normally be understood to mean the depot formulation of paliperidone palmitate. However, in claims 33 and 34, the medicament in the preamble must contain the distinct loading and maintenance doses in "medicament form."

[158] Janssen's experts uniformly agreed that "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.

[159] The parties disagree on the proper construction of these "Swiss-type" claims. Teva urges the Court to look past the form of the claims, and interpret them as use claims covering the same subject matter as claims 17 to 32 (*Novartis Pharmaceuticals Canada Inc v Cobalt*

Pharmaceuticals Company, 2013 FC 985 at para 101, aff'd 2014 FCA 17; *Pfizer Canada Inc v Apotex Inc*, 2007 FC 971 at paras 32-35, aff'd 2009 FCA 8).

[160] Conversely, Janssen submits that claims 33 to 48 are akin to purpose-limited product claims, capable of direct infringement by a generic company if the product is manufactured and sold for the claimed treatment (*Hospira*, above, at paras 268-318).

[161] The proper meaning of the claims must be determined having regard to the words of the claims when construed purposively through the eyes of the POSITA in light of the specification and the common general knowledge at the relevant date. Claims 33 to 48 claim the "use of paliperidone as paliperidone palmitate" for the preparation (claim 33) or in the manufacture (claim 34) of a medicament, wherein the medicament comprises loading and maintenance doses. That said, the claims also include as essential elements:

> i. the dosing schedule of days 1, 8, and monthly thereafter;
>
> ii. specific dose amounts of 150, 100, and 75 mg-eq for non-renally impaired patients, and 100, 75, and 50 mg-eq for renally impaired patients; and
>
> iii. injection sites of the deltoid (loading doses on days 1 and 8) and deltoid or gluteal (maintenance doses).

[162] If the dosing schedule and dose amounts were not essential elements, the claims would amount to claims for the manufacture of a depot formulation of paliperidone palmitate. However, these claims' essential features go beyond simple manufacture of a depot formulation and additionally prescribe a specific dosing schedule, specific dose amounts, and specific injection sites.

[163] The Swiss-type claims are capable of infringement if the medicament is adapted for administration to a psychiatric patient in need of treatment, according to the claimed dosing regimen (*Hospira* at para 318, aff'd *Hospira FCA*, above, at paras 25-29).

VII. Obviousness

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

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

[166] The four part obviousness framework was laid out by the Supreme Court of Canada in *Sanofi*, above, 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?

[167] 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 para 68). In

such situations, the following non-exhaustive factors should be taken into account at the fourth step of the obviousness inquiry (*Sanofi* at paras 69-71):

> 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?

[168] 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,* above, at para 85; *Tensar Technologies, Limited v Enviro-Pro Geosynthetics Ltd*, 2019 FC 277 at para 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 para 70). 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 at para 44 [*Bristol-Myers Squibb*]).

[169] The Court must be wary of hindsight bias from expert witnesses. It is not fair to a person claiming to have invented a combination invention to break the combination down into its parts and find that, because each part is well known, the combination is therefore obvious (*Bridgeview*

Manufacturing Inc v 931409 Alberta Ltd (Central Alberta Hay Centre), 2010 FCA 188 at para 51 [*Bridgeview*]). 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).

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

[171] Dr. Kwon opined that the formulation aspects of the Asserted Claims are not inventive. All formulation limitations in the dependent claims were either disclosed in Canadian Patents No. 2,309,629 [the 629 Patent] and 2,326,691 [the 691 Patent], or would have been routinely selected by the POSITA in light of their common general knowledge. Any work required to arrive at the formulations in the 335 Patent would have been straightforward and routine.

[172] Janssen did not file any expert evidence to suggest the formulation aspects of the claims were inventive, so Dr. Kwon's evidence is uncontradicted. Janssen submits that Dr. Kwon's opinion on obviousness should be given no weight because he considered some inadmissible art in forming his opinion. I disagree. Considering Janssen's 629 and 691 Patents 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.

[173] Similarly, the 629 Patent disclosed the use of depot formulations of paliperidone palmitate to treat schizophrenia and schizoaffective disorder. The limitation to these specific disorders in claims 15, 16, 31, 32, 47, and 48 is no different from the prior art.

[174] The validity of dependent claims 3 to 16, 19 to 32, and 25 to 48 therefore rises or falls with the inventiveness of the dosing regimens in claims 1, 2, 17, 18, 33, and 34.

[175] The POSITA and common general knowledge have been described in detail above, so the next step is to identify the inventive concept of each independent claim.

A. *The inventive concept*

[176] Teva submits that at this stage, the inquiry is focused on the inventive concept of the claim in question, not some generalized inventive concept derived from the specification as a whole (*Ciba Specialty Chemicals Water Treatments Limited v SNF Inc*, 2017 FCA 225 at para 74 [*Ciba*]). Because the experts disagreed on the inventive concept of the claims, Teva submits that searching for an inventive concept is a distraction the Court should avoid by simply pursuing the alternative course of construing the claims, as sanctioned by the Supreme Court of Canada in *Sanofi*.

[177] Teva's position, as supported by Dr. Bergstrom, is that all asserted claims, when purposively construed, are for a dosing regimen for a depot formulation of paliperidone palmitate for the treatment of schizophrenia. The dosing regimen has two aspects, a loading dose regimen and a maintenance dose regimen, and specifies the dose amount, dosing schedule and injection

sites. Claims 2, 18, and 34 include a modified dosing regimen for patients with renal impairment. The three claim sets describe the dosing regimen in terms of prefilled syringes, use of a dosage form, and Swiss-type claims, respectively.

[178] Janssen submits the inventive concept of claims 1, 17, and 33 is a "standardized and optimized" dosing regimen of depot formulations of paliperidone for psychiatric patients in need of treatment for schizophrenia, which quickly and safely reaches and maintains potentially therapeutic plasma concentrations of paliperidone. The inventive concept of claims 2, 18, and 34 is the same, but for patients with renal impairment.

[179] Dr. Agid referred to the dosing regimens as "preferred and standardized" and "one size fits all" – applicable to all patients. Dr. Ereshefsky defined the inventive concept as "standardized and optimized" dosing regimens.

[180] Referring to the claimed dosing regimens as "standardized and optimized" sets the bar for the inventive concept too high, and is not supported by the claim language or the disclosure. While there is no need to look to the disclosure to identify the inventive concept in this case, even if I do consider the passages relied on by Janssen's experts, they do not support Janssen's position.

[181] Drs. Agid, Bies, and Ereshefsky all referred to the following passage from the

"Background of the Invention" section of the 335 Patent to say that the claimed dosing regimens are optimized:

> Due to the challenging nature of ensuring an optimum plasma concentration-time profile for treating patients with paliperidone it is desirable to develop a dosing regimen that fulfills this goal in patients in need of treatment.

[182] Clearly the inventors sought to develop a dosing regimen that ensures an optimum plasma concentration-time profile for treating patients with paliperidone, but this does not imply that the claimed dosing regimen is in fact optimized. The claimed dosing regimen is not specifically described anywhere in the disclosure.

[183] Dr. Ereshefsky selectively pieced together references in the disclosure to each element of the claimed dosing regimen to arrive at his conclusion that the regimen is "standardized and optimized." He focused on Figure 2, which shows observed and popPK simulated plasma concentrations for a dosing regimen of 150 mg-eq in the deltoid on day 1, followed by 100 mg-eq in the deltoid or gluteal on days 8, 36, and 64. He then combined this figure with the following poorly worded quote to conclude that the optimal maintenance dose is 75 mg-eq: "most preferably the maintenance dose initially will be about 50 mg-eq, or more preferably the maintenance dose initially will be about 75 mg-eq" (335 Patent p 12, lines 20-21).

[184] With respect to the regimen being "standardized" or "one size fits all," the inventors contemplated that the maintenance dose can range from 25 mg-eq to 150 mg-eq, and should be selected to maintain therapeutic plasma concentrations. The POSITA would "understand that the maintenance dose may be titrated up or down in view of the patients condition" (335 Patent p 12,

lines 23-25). When pressed on cross-examination as to how he came up with the term "standardized" to describe the inventive concept, Dr. Ereshefsky stated that this concept is found in the language of claims, and "[t]he word isn't there but the content is." I find this explanation overstates and contradicts the plain language of the claims.

[185] I find that the inventive concept is a safe and effective dosing regimen using a depot formulation of paliperidone designed to quickly attain, and maintain, therapeutic plasma concentrations of paliperidone for treating patients with schizophrenia. This definition of the inventive concept closely aligns with Teva's proposed inventive concept based on the claims as construed. As submitted by Teva, the dosing regimens include loading doses and maintenance doses, and specify the dose amount, dosing schedule and injection site.

[186] This approach finds support in the expert evidence of Dr. Bergstrom and Dr. Bies, the latter having expressly defined the inventive concept as follows:

> The inventive concept of claims 1, 17 and 33 of the 335 Patent is a dosing regimen, which, using a depot formulation of paliperidone as paliperidone palmitate formulated as an aqueous nanoparticle suspension for psychiatric patients in need of treatment for schizophrenia, schizoaffective disorder or schizophreniform disorder, quickly reaches and maintains plasma concentrations of paliperidone within a potentially therapeutic range.
>
> [emphasis added]

[187] Accordingly, 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, and 33:

- 150 mg-eq of paliperidone as paliperidone palmitate injected into the deltoid on day 1;
- 100 mg-eq of paliperidone as paliperidone palmitate injected into the deltoid on day 8 ± 2 days;
- 75 mg-eq of paliperidone as paliperidone palmitate injected into the deltoid or gluteal monthly ± 7 days thereafter.

[188] 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, and 34.

B. *Differences between the state of the art and the inventive concept*

[189] During the course of trial, the Court determined that Teva failed to establish that certain documents had become available to the public as of December 19, 2007 so as to become part of the state of the art. Portions of the clinicaltrials.gov records that were published after December 19, 2007, the Kramer Abstract, and the Kramer document, were ruled inadmissible. Aspects of Dr. Bergstrom and Dr. Kwon's expert reports that relied on these references have not been taken into consideration.

[190] Teva primarily relies on the 629 Patent and the Citrome article as relevant prior art for obviousness. Citrome is a review article published in April 2007 that summarizes information about ongoing and completed paliperidone clinical trials. Data in the paper was compiled from the clinicaltrials.gov website, and includes information from 15 studies using an extended release

oral formulation, and seven studies using depot intramuscular formulations. Of the depot formulation studies listed, six were phase 3 studies, and one was a phase 1 study.

[191] Citrome does not set out any particular information about the formulation, simply stating that the clinical trials will use a "depot intramuscular formulation."

[192] Having considered the Citrome article and the corresponding information from clinicaltrials.gov that was available as of the relevant date, the following information was disclosed in the prior art:

- Phase 3 trials investigating paliperidone depot injection doses of 25, 50, 75, 100, and 150 mg-eq were ongoing;
- One phase 3 trial was investigating fixed dosing (same dose administered on each dosing day) in the gluteal on days 1, 8, 36, and 64;
- One phase 3 trial was investigating monthly dosing;
- Several phase 3 trials were investigating dosing regimens with fixed doses;
- One phase 3 trial was investigating a dosing regimen with flexible doses where the dose was determined for each individual patient by the investigator;
- One phase 1 trial and one phase 3 trial were evaluating the safety and tolerability of injections into the deltoid or gluteal muscle. The phase 3 trial hypothesis was that there would be no difference in safety and tolerability between gluteal and deltoid injections.

[193] The 629 and 691 Patents disclose a target paliperidone plasma concentration range of 10 to 100 ng/mL. The 691 Patent also discloses aqueous depot formulations of paliperidone as paliperidone palmitate that are therapeutically effective for approximately one month.

[194] Dr. Bergstrom stated in his report that the POSITA would have noted that many of the above trials were phase 3 trials, meaning that Janssen must have had sufficiently positive phase 2 results, and the development of the dosing regimen was in its final stages. However, on cross-examination, Dr. Bergstrom qualified his opinion, stating that the trials indicate that the drug developers *may* be at the end of their development, but phase 3 trials are not always successful. If phase 3 trials fail, additional development work is needed. Dr. Bergstrom further admitted that depot formulation development is a long and difficult enterprise because doses are given infrequently, and therefore it takes a long time to assess clinical trials.

[195] In Dr. Bergstrom's opinion, the only difference between the inventive concept of the 335 Patent claims and the prior art is the specific loading and maintenance dose amounts and the injection sites. Because Citrome disclosed a phase 3 trial investigating dosing on days 1, 8, 36, and 64, there is no difference between the prior art and the claimed dosing schedule. Dr. Ereshefsky acknowledged that this was the only definite loading dose schedule for a depot formulation of paliperidone palmitate disclosed in the prior art.

[196] On cross-examination, Dr. Bergstrom explained that the POSITA would know that flexibility in the dosing schedule is needed when designing a dosing regimen for depot antipsychotics, and the claimed dosing windows are merely practical. Nevertheless, the dosing windows are essential elements of the claims, and were not disclosed in the prior art.

[197] As submitted by Janssen, I find that the differences between the state of the art and the inventive concept are:

- 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.
- The specified dose amounts of the claimed regimens;
- A loading dose regimen administered into the deltoid muscle;
- Maintenance doses administered interchangeably in the deltoid or gluteal muscle;
- Dosing windows of ± 2 days (second loading dose) and ± 7 days (maintenance doses); and
- An adjusted regimen for patients with renal impairment.

C. *Do the differences constitute steps that would have been obvious to the POSITA?*

[198] 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 69-71.

[199] Essentially, Teva argues that the prior art discloses dosing regimens for paliperidone palmitate depot formulations that include five dose amounts (25, 50, 75, 100, and 150 mg-eq), two injection sites (deltoid and gluteal), and two dosing schedules (monthly, or days 1, 8, and monthly thereafter). To get from here to the claimed dosing regimen, the POSITA would simply undertake routine testing to arrive at the claimed combinations of dose amount, dose schedule, and injection sites.

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

> (1) Is it more or less self-evident that what is being tried ought to work? Are there a finite number of identified predictable solutions known to persons skilled in the art?

[201] Drs. Bergstrom and Ereshefsky agreed that the POSITA would have needed to understand the pharmacokinetic profile of the paliperidone depot formulation in order to design a dosing regimen. As of the relevant date, the necessary pharmacokinetic data in humans was not disclosed in the prior art. Determining the rate of release of paliperidone from the depot formulation would at least require testing in animal models followed by testing in humans to confirm and adjust the dosing as necessary.

[202] Dr. Bergstrom opined that the POSITA would have known that a loading dose was required to reach steady state plasma concentrations quickly, so they would have focused on the loading dose regimen of doses on days 1 and 8 disclosed in Citrome. However, the POSITA would have known from their common general knowledge that loading doses can take the form of a higher initial dose, more frequent initial dosing, or both. In Citrome, the only trial that clearly disclosed a loading dose regimen used fixed dosing, whereas the claimed dosing regimen uses two different loading doses, and a lower maintenance dose.

[203] Even if the POSITA decided to pursue a loading dose regimen, they would have to run clinical trials to evaluate the safety and efficacy of a large number of variables including fixed

doses, variable doses, and injection sites. While I agree with Teva that the number of dosing regimen variables is finite, I am not satisfied that based on the state of the art there were a finite number of *identified, predictable* solutions. As Dr. Bergstrom himself pointed out, studies were needed to simply understand paliperidone's pharmacokinetic profile and therapeutic plasma concentration range prior to undertaking any dosing regimen design.

[204] Further, while Citrome disclosed a range of dose amounts up to and including 150 mg-eq, and a loading dose regimen with injections on days 1 and 8, the paper did not disclose whether the combination of this amount on these days was safe and effective. Although the POSITA may have assumed that phase 2 trials had shown to promise in order for the researchers to move ahead with a phase 3 trial using this schedule and dose amounts, it would not have been self-evident that some combination of the disclosed dose amounts, dosing schedule, and injection sites would quickly and safely achieve therapeutic plasma concentrations of paliperidone.

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

[205] I agree with Teva that the POSITA need not be capable of conducting the same experiments that the inventors did to reach the claimed invention (Hospira FCA at para 94). That said, 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*, above, at para 44).

[206] Dr. Bergstrom walked through the steps the POSITA would have taken. First, as described above, they would conduct testing to understand the pharmacokinetic profile of the paliperidone depot formulation. The POSITA would know that loading dosing would be required for optimal treatment, because this type of depot formulation takes several months to reach steady state with monthly injections alone. Using the plasma concentration range of 10 to 100 ng/mL identified in the 629 Patent, and the dose amounts and schedules disclosed in Citrome, the POSITA would then conduct a small trial to test a number of dosing regimens to identify which one resulted in optimal plasma concentrations of paliperidone. The POSITA would know that the loading dose amounts would be greater than the maintenance dose amounts, so they would focus on the higher end of the range for the loading dose—100 to 150 mg-eq—and the lower end of the range for the maintenance dose—25 to 100 mg-eq. Dr. Bergstrom does not provide a reasonable explanation for his opinion on this point.

[207] Dr. Bergstrom also opined that the POSITA would have anticipated that injection into the deltoid would result in faster release and absorption of the active ingredient, and therefore would have investigated the deltoid as a possible injection site for the loading dose injections in order to quickly get the plasma concentrations within the therapeutic range.

[208] The simplicity of Dr. Bergstrom's approach is belied by his agreement with Dr. Ereshefsky that in order to design a dosing regimen, the POSITA would first have needed to run clinical studies to determine the pharmacokinetic profile of paliperidone injection. While the doses and schedules disclosed in Citrome would have been useful information, no results are

included, and aside from the fact that these are mostly phase 3 trials, there is no indication of whether the doses being investigated are safe or effective.

[209] In fact, the only study disclosed in Citrome where a loading dose regimen was definitely being used had a fixed dosing regimen, that is, each loading and maintenance dose amounts were the same. Nothing in Citrome points the POSITA towards a variable dosing regimen such as that claimed in the 335 Patent. Before Dr. Bergstrom's POSITA has conducted any clinical trials, they have made several steps in the right direction towards the claimed invention with little to no explanation of how. While the POSITA would have been aware that loading dose regimens using a higher starting dose amount were possible, this would simply have been another factor that the POSITA would have to consider when conducting their own experiments.

[210] As noted by Dr. Ereshefsky, the safe and effective plasma concentration selected by the inventors of the 335 Patent was 7.5 to 40 ng/mL, based on back calculations from phase 3 extended release oral paliperidone studies and D2 occupancy studies in healthy human volunteers. Clearly the plasma concentration range disclosed in the 629 Patent needed work and refinement. This is yet another step required as a prerequisite to designing a dosing regimen to quickly achieve and maintain plasma concentrations within this safe and effective range.

[211] With respect to the injection sites, the POSITA would have known that absorption is faster from the deltoid than the gluteal due to greater blood flow. Dr. Vermeulen acknowledged on cross-examination that the inventors may have expected injection in the deltoid to result in a faster initial increase in plasma concertation, but the purpose of their injection site study was to

establish interchangeability of injection sites rather than faster increase in plasma concentration from deltoid injections. Dr. Ereshefsky explained that because the rate limiting step is release of the active drug from the depot site, the difference in blood flow at the two injection sites may have no meaningful difference for a given drug. Therefore, the POSITA would not necessarily have anticipated faster release from the deltoid as advanced by Teva, and the injection site variable would have required exploration.

[212] Regardless of Dr. Bergstrom's opinion that phase 3 trials indicate to the POSITA that phase 2 trials had positive results, phase 3 trials are not always successful. Tellingly, Dr. Bergstrom admitted that depot formulation development is a long and difficult enterprise. This evidence is consistent with the actual course of conduct. Janssen began its phase 3 studies investigating fixed doses of 25 to 150 mg-eq administered on days 1, 8, and monthly thereafter in December 2004; three years prior to the claim date.

[213] Teva submits that Janssen's experts focused on the wrong question of what the inventors did to arrive at the claimed invention. I agree that the obviousness inquiry is focused on how the POSITA would have acted in the light of the prior art, however, evidence of what the inventors did may be considered under this factor of the obvious to try inquiry.

[214] Contrary to Teva's submission that the failure of PSY-3003 and PSY-3004 was a result of Janssen taking a wrong turn, this course of conduct is consistent with Dr. Bergstrom's testimony that phase 3 trials can fail, and if they do fail, the depot development process requires further work. Even with the knowledge of all aspects of the paliperidone palmitate clinical trials

they had run up to that point, the inventors still had to overcome further hurdles in the development process.

[215] In part, Janssen overcame these hurdles using Dr. Samtani's popPK modeling to account for covariate effects and further refine the dosing regimen. Dr. Bies gave evidence that Janssen's popPK modeling was elegant and rigorously implemented. I acknowledge Teva's position that modeling work does not form part of the claimed invention, and is but one tool the POSITA could have used to develop a safe and effective dosing regimen. The POSITA need not have been able to develop the same quality of popPK models as Dr. Samtani for the invention to be obvious. However, this does not mean that the effort required to achieve the invention was therefore routine.

[216] Counsel for Teva analogized the facts of this case to the obviousness finding in *Ciba*. The inventive concept at issue in *Ciba* was the use of an "effective" rigidifying amount of a solution for rigidifying a slurry deposit. The Federal Court had found that the common general knowledge included knowledge that slurries could be treated using an aqueous solution of water-soluble polymers. The Federal Court's reasoning, as explicitly affirmed by the Federal Court of Appeal, is found at paragraph 94:

> The Skilled Person would have gone directly and without difficulty to the step of using a minimum dosage of polymer to achieve the level of rigidification of the slurry deposit for the job. It is routine for the Skilled Person to decide, *inter alia*: the nature of the polymer; its form and dosage; and the point of addition to the slurry line. Thus, applying an "effective" amount is obvious, as the Skilled Person would continue to apply the necessary polymer to achieve the necessary outcome and discontinue application once overdosing occurred.

[217] Teva submits that in this case, Citrome and the 629 Patent point the way, and the POSITA need only conduct routine testing to arrive directly at the claimed dosing regimen. I disagree. The context of the two inventions are quite different. Applying an "effective" amount of a polymer to a mining slurry is quite unlike developing a safe and effective dosing regimen that requires plasma concentrations maintained within a particular range. Simply discontinuing application once overdosing occurs is not a viable option in pharmaceutical development.

[218] Having considered the composite POSITA and their common general knowledge as defined, in light of the numerous steps required to even begin evaluating possible dosing regimens using the dose amounts, dosing schedules, and injection sites disclosed in Citrome, the POSITA would have had to carry out prolonged and arduous experimentation to the point that the trials would not be considered routine. The effort required to reach the claimed dosing regimen in light of the state of the art and the common general knowledge was substantial.

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

[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.

D. *Conclusion on obviousness*

[220] Teva acknowledges that the inventors were likely talented and driven, but ultimately they were carrying out "skilled work" using standard tools to address issues commonly encountered in pharmaceutical development. As such, in Teva's submission, the work conducted does not rise to the level of "inventive" and does not deserve patent protection (*Amgen Canada Inc v Apotex Inc*, 2015 FC 1261 at paras 84-85 and 101).

[221] Having considered all of the expert evidence and the prior art, I am not satisfied that Teva has met its burden. While individually or together, the formulation elements in the dependent claims are not inventive, each of the Asserted Claims of the 335 Patent incorporates one of the dosing regimens as essential elements. Teva primarily relies on Dr. Bergstrom's expert opinion evidence that the claims are obvious. His evidence is weakened, however, by the unexplained leaps he makes from the state of the art to the place where he says the POSITA would start their routine trials (*Bridgeview*, above at para 53).

[222] Absent knowledge of the claimed dosing regimen, these leaps would not have been possible, and I therefore agree with Janssen that Dr. Bergstrom improperly used hindsight in arriving at his conclusion. He broke the dosing regimen down into its component parts, and because many of these parts were individually disclosed in Citrome, he concluded that the claimed combination was therefore obvious (*Bridgeview* at para 51).

[223] 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.

[224] I find that the combination of the claimed dosing regimen elements is inventive, and the Asserted Claims of the 335 Patent are not obvious.

VIII. Infringement

[225] Pursuant to section 6 of the *Regulations*, Janssen seeks a declaration that the making, constructing, using, or selling of Teva's paliperidone palmitate product in accordance with its ANDS would infringe the 335 Patent. Infringement is any act that deprives the patentee and their legal representative of the exclusive right, privilege, and liberty of making, constructing and using the invention and selling it to others (*Patent Act*, s 42). Janssen bears the burden of proving infringement (*Monsanto Canada Inc v Schmeiser*, 2004 SCC 34 at para 29 [*Monsanto*]).

[226] To determine whether a patent claim is infringed, having purposively construed the claims and identified essential claim elements, the Court must determine whether the allegedly infringing product falls within the scope of the claims (*Free World Trust* at paras 48-49). There is no infringement if an essential element is different or omitted, but there may still be infringement if a non-essential element is substituted or omitted (*Free World Trust* at para 31).

[227] It is well established that allegations of non-infringement under the *Regulations* refer only to actions of the "second person"—in this case Teva—and infringement in this context

means both direct infringement and indirect infringement by inducement or procurement (*Aventis Pharma Inc v Pharmascience Inc*, 2006 FCA 229 at paras 55-59). Absent influence by Teva, infringing acts of third parties do not ground a finding of infringement under the *Regulations* (*Novopharm Limited v Sanofi-Aventis Canada Inc*, 2007 FCA 167 at paras 10-11 [*Novopharm*]).

[228] As a preliminary point applicable to all claims, I am satisfied that the Teva product incorporates all formulation elements of the 335 Patent.

[229] Teva's only formulation related non-infringement argument is a rather weak submission that each of the proposed Teva products will contain more than 110% of the amount of paliperidone palmitate indicated. Dr. Rabinow explained in his report that in line with the commonly known manufacturing principle of "overfill," increased amounts are included in each syringe to ensure that the patient actually receives the intended amount of paliperidone palmitate following administration. The claims use the language "dose of the depot formulation comprising about [quantity] mg-eq of paliperidone as paliperidone palmitate" (emphasis added). In my view, the dose referred to is the dose to be delivered to the patient. This interpretation is consistent with Teva's PM and packaging that lists the doses of paliperidone palmitate as 150, 100, 75, 50, and 25 mg-eq, not the increased amounts that account for overfill.

[230] Based on the Certified Product Information Document submitted by Teva to Health Canada, and the uncontested evidence of Dr. Rabinow, Janssen has met its burden of establishing that Teva's paliperidone palmitate product will incorporate all formulation elements of the 335

Patent, including amounts of active and inactive ingredients, pH, particle size, and choice of inactive ingredients.

[231] Similarly, claims 15, 16, 31, 32, 47, and 48 are limited to treatment of patients with schizophrenia or schizoaffective disorder only. The Teva product is indicated for treatment of both disorders, so if the independent claims from which they depend are infringed, claims 15, 16, 31, 32, 47, and 48 will be infringed.

[232] Therefore, the heart of the infringement dispute lies in independent claims 1, 2, 17, 18, 33, and 34. I will consider direct and indirect infringement of these claims.

A. *Direct Infringement*

[233] Janssen submits that Teva will directly infringe claims 1 to 16 and 33 to 48 by selling its paliperidone palmitate product. Janssen's position is that both of these claim sets are product claims and therefore no active use is required to support a finding of infringement

[234] Teva submits that because it does not prescribe or administer medications, it cannot infringe these claims, as they all require administration in accordance with the claimed dosing regimens. Alternatively, Teva submits that to the extent the Court determines that administration to patients is not an essential element of the first and third claim sets, Teva will not directly infringe as it will not direct use in accordance with the claimed dosing regimens.

[235] As previously noted, the parties agree that Teva will not directly infringe "use" claims 17 to 32, and the Court need only consider inducing infringement in respect of these claims.

[236] Janssen relies on Justice Phelan's decision in *Hospira* in support of its position. Some of the asserted claims in that case were directed towards a medicine for use in performing adjunctive therapy with methotrexate on a patient with rheumatoid arthritis (*Hospira* at Appendix B, claims 17 and 18). Hospira's PM stated that Inflectra was indicated for "use in combination with methotrexate for the reduction in signs and symptoms, inhibition of the progression of structural damage and improvement in physical function in adult patients with moderately to severely active rheumatoid arthritis."

[237] Justice Phelan found that Inflectra was to be used in combination with methotrexate. The fact that Hospira itself did not did not perform the adjunctive therapy was insufficient to ground Hospira's non-infringement argument. Aside from four dependent claims, the Federal Court of Appeal dismissed Hospira's appeal as it related to infringement (*Hospira FCA* at paras 116-119).

[238] In Janssen's submission, evidence that a generic proposes to manufacture and sell their pharmaceutical preparations for administration according to the patented dosing regimen is sufficient to show direct infringement of these types of claims (*AlliedSignal Inc v DuPont Canada Inc* (1993), 50 CPR (3d) 1 (FCTD) at 19, rev'd in part on other grounds, but expressly affirming the trial judge's infringement analysis (1995) 61 CPR (3d) 417 (FCA)).

[239] With respect to the dosing schedule, dose amounts, and injection sites, Janssen submits that the Teva PM specifies the approved indications and dosage and administration instructions, which include administration according to the claimed dosing regimens of the 335 Patent. Janssen's relies on this Court's finding in *Hospira* that a PM is persuasive evidence of product use in a direct infringement inquiry (*Hospira* at para 302). Further, the package insert and product labels will contain dosing information.

[240] The inquiry is whether the Teva product will incorporate all essential elements of any of the claims if Teva sells its product in Canada. I will first consider claim 1 based on its constituent elements. The essential elements of the claim are bolded, followed by relevant evidence connected to Teva's paliperidone palmitate product.

[241] **Prefilled syringes containing a depot formulation of paliperidone as paliperidone palmitate formulated as an aqueous nanoparticle suspension:** The Teva PM and product labels indicate that the Teva product comes as individual, pre-filled syringes containing a prolonged-release injectable suspension of paliperidone palmitate. The product labels list water as a non-medicinal ingredient and state that the syringe contains a prolonged-release suspension. As noted above, the Teva product incorporates the formulation aspects of all claims.

[242] **For administration by intramuscular injection to a psychiatric patient in need of treatment for schizophrenia, schizoaffective disorder, or schizophreniform disorder:** The product labels state that the product is "for intramuscular use only" and the PM identifies the route of administration as "intramuscular injection." Dr. Agid gave evidence that if the Teva

product came to market, the paliperidone palmitate suspension would be administered intramuscularly.

[243] The product labels give dosing instructions for adults with schizophrenia and schizoaffective disorder. The Teva PM states that the Teva product is indicated for the treatment of schizophrenia and schizoaffective disorder. Mr. Boughner, Teva's Senior Director of Commercial Management, acknowledged on cross-examination that the Teva PM informs health care professionals that the Teva product is for treatment of both disorders.

[244] **A first loading dose of about 150 mg-eq of paliperidone injected into the deltoid on treatment day 1:** Teva will sell prefilled syringes containing a dose of about 150 mg-eq of paliperidone palmitate, taking into consideration overfill. The Teva PM states that for schizophrenia and schizoaffective disorder patients, the recommended initiation regimen starts with a dose of 150 mg. As construed, a loading dose is a dose used to quickly bring the blood plasma concentration of the drug into the desired therapeutic range. The Teva PM states that the initiation regimen doses are administered "in order to attain therapeutic concentrations rapidly." Therefore, this dose as defined in the PM is a loading dose.

[245] The recommended initiation regimen in the Teva PM specifies that the 150 mg initiation dose is to be administered into the deltoid muscle on treatment day 1. Similarly, the product labels state "Day 1: 150 mg administered in the deltoid muscle" for treatment of schizophrenia and schizoaffective disorder.

[246] **A second loading dose of about 100 mg-eq of paliperidone injected into the deltoid on treatment day 8 ± 2 days:** Teva will sell prefilled syringes containing a dose of about 100 mg-eq of paliperidone palmitate, taking into consideration overfill. The Teva PM specifies a dose of 100 mg on day 8 administered in the deltoid muscle as part of the initiation regimen, and the product labels state "Day 8 (one week later): 100 mg administered in the deltoid."

[247] The "Missed Doses" section of the Teva PM teaches that patients may be given the second dose up to 4 days before or after the one week time point. While this dosing window is wider than that claimed, the Teva PM still recommends that the second initiation dose be given one week after the first, and in any event, 2 of the 4 days on either side of the recommended date fall within the claimed dosing schedule.

[248] **Continuous maintenance doses of 75 mg-eq of paliperidone injected into the deltoid or gluteal monthly ± 7 days thereafter:** Teva will sell prefilled syringes containing a dose of about 75 mg-eq of paliperidone palmitate, taking into consideration overfill. As construed, this element is not a single syringe, but rather multiple syringes for use on a continuous maintenance schedule. Teva will sell multiple prefilled syringes which include syringes with 75 mg-eq of paliperidone palmitate.

[249] With respect to the dosing schedule, the Teva PM repeatedly refers to a "monthly maintenance dose." As with the construction of this claim term, a reasonable reading of the term "monthly maintenance dose" in the Teva PM is that maintenance doses are to be administered

according to a continuous schedule. The "Missed Doses" section of the Teva PM states that patients may be given the monthly dose up to 7 days before or after the monthly time point.

[250] [redacted]

[251] The Teva PM and product labels recommend that the monthly maintenance doses can be administered in either the deltoid or gluteal muscle.

[252] To conclude, Janssen has established that the Teva product will incorporate all essential elements of claim 1 of the 335 Patent. Should Teva come to market and sell its paliperidone palmitate prefilled syringes, it will infringe the 335 Patent. I cannot accept Teva's position that it will not directly infringe as it will not direct use in accordance with the claimed dosing regimens. As concisely put by counsel for Janssen, "the capable, approved and intended use for the Teva Product as specified in the Teva Product Monograph incorporates all dosing and administration elements."

[253] The Teva PM teaches that the prefilled syringes to be sold by Teva can be administered in combination according to the claimed dosing regimen. While this information may not rise to the level of "instructions to infringe" sufficient to induce practitioners to prescribe and use the syringes according to the claimed dosing regimen, it is sufficient to establish direct infringement of the product claims.

[254] The Teva PM also teaches that its prefilled syringes can be administered according to other, non-infringing dosing regimens. However, Teva need not direct that the claimed dosing regimen is the only regimen, or even the recommended regimen, by which its syringes should be administered. Sale of prefilled syringes adapted for administration in accordance with the claimed dosing regimen, as taught in the Teva PM, will deprive Janssen of the full enjoyment of the 335 Patent monopoly (*Monsanto*, above, at para 34). Actual use of the syringes in accordance with the claimed dosing regimen is not required.

[255] The same conclusion follows for claim 2 based on the dose adjustment for patients with renal impairment in the Teva PM. Based on the earlier discussion of the formulation and indication limitations in the dependent claims, Teva will directly infringe claims 3 through 16.

[256] Consistent with the construction of the third claim set as use of paliperidone as paliperidone palmitate for the preparation/manufacture of a medicament adapted for administration according to the claimed dosing regimen, Teva will also directly infringe claims 33 to 48 by making and/or selling its paliperidone palmitate product, along with its PM teaching that the prefilled syringes can be administered according to the claimed dosing regimen.

B. *Indirect Infringement by Inducement*

[257] In applications under the old Patented Medicines (Notice of Compliance) regime, the relevant inquiry was whether allegations of non-infringement were justified. Pursuant to the September 2017 amendments, proceedings under the *Regulations* are full patent actions. In inducement cases under the pre-September 2017 regime, the Court noted that should the generic come to market and begin inducing infringement, the brand owner would still have recourse to an action for infringement (see, for example, *Bayer Inc v Pharmaceutical Partners of Canada Inc*, 2015 FC 388 at para 33; *Lundbeck Canada Inc v Ratiopharm Inc*, 2009 FC 1102 at para 383 [*Lundbeck*]). This is no longer the case under the new regime.

[258] From approximately 2006 onwards, Federal Court jurisprudence clearly recognizes that mere sale by a generic of an old drug for an old use will not constitute infringement of a patent directed to a new use for that drug unless "something more" than sale is established. "Something more" may be inducement or procurement (*Novopharm*, above, at paras 10-11). The patentee must establish infringement by a third party and a nexus linking the third party's infringing acts to the generic producer. The PM plays a key role in determining inducement (*AB Hassle v Canada (Minister of National Health and Welfare)*, 2002 FCA 421 at para 55).

[259] The "new use for a known compound" cases are fairly consistent that "something more" is established where the PM makes reference to the "new" infringing use, either directly or inferentially (*Genpharm Inc v Canada (Minister of Health)*, 2002 FCA 290; *AB Hassle v Genpharm Inc*, 2003 FC 1443 [*AB Hassle*], aff'd 2004 FCA 413 [*AB Hassle FCA*]; *Aventis*

Pharma Inc v Apotex Inc, 2005 FC 1381 [*Aventis Pharma*]; *Abbott Laboratories Limited v Canada*, 2006 FC 1411 [*Abbott Laboratories*], aff'd 2007 FCA 251).

[260] Where the PM clearly only references the "old" non-infringing use, allegations of non-infringement were made out (*AB Hassle v Canada (Minister of National Health and Welfare)*, 2001 FCT 1264, aff'd 2002 FCA 421*; Novopharm*). The same is true in cases with "combination therapy" claims: where the PM only directly refers to monotherapy with one of the required components of the combination, allegations of non-infringement succeeded (*Lundbeck*, above).

[261] These cases typically did not consider the tripartite test for inducement, but rather focused on infringement by a third party and some nexus to the generic company, typically established by references made in the PM. Notably, the second and third prongs of the inducement test, influence by the generic on the infringing party and knowledge that this influence will result in infringement, appear not to have been fully considered.

[262] Conversely, in more recent cases, the Court has scrupulously evaluated the three prong test for inducement from *Corlac Inc v Weatherford Canada Inc*, 2011 FCA 228 at paragraph 162 [*Corlac*], with particular focus on the second prong: "the completion of the acts of infringement must be influenced by the acts of the alleged inducer to the point that, without the influence, direct infringement would not take place" (*Bayer Inc v Pharmaceutical Partners of Canada Inc*, 2015 FC 797 at para 49 [*Bayer*], aff'd 2016 FCA 13; *Janssen Inc v Apotex Inc*, 2019 FC 1355 at paras 232-234 [*Janssen*]; *Allergan Inc v Canada (Health)*, 2011 FC 1316 at paras 145-171).

[263] In particular, in *Bayer*, Justice Strickland reiterated the requirement for the patentee to show that but for the influence of the second person, the direct infringement would not have taken place (*Bayer*, above, at paras 49 & 80). Similarly, in *Janssen*, Justice Phelan highlighted the "but for" requirement and stated there is a "high bar" to meet the test for infringement by inducement (*Janssen*, above, at paras 232-234).

[264] The "but for" influence required in the second prong of the *Corlac* test requires a higher threshold for establishing inducement than was applied in the earlier cases. While the law is settled that inducement is required, the "but for" test is quite different from an "encouragement to infringe" (*Abbott Laboratories,* above, at para 40), "subtle reference" to the infringing use (*AB Hassle*, above, at para 155), or "attempting to induce others to infringe" (*AB Hassle FCA*, above, at para 17).

[265] Where the Court has considered the test for inducement from *Corlac*, the outcome has turned on the specific references in the PM. In *Bayer*, while the PM stated that the generic company's moxifloxacin product was "compatible" with sodium chloride solutions, the PM actually recommended *against* the infringing co-administration of moxifloxacin and sodium chloride solutions. Conversely, in *Hospira* and *Janssen*, the PMs specifically recommended the infringing combination therapies.

[266] Another important factor in all of these cases is the wording of the claims themselves. As noted by Justice Phelan in *Janssen*, to establish inducement, the alleged inducer must induce infringement of all essential elements of the asserted claims. Where the claims are directed

towards a new use for a known compound, the PM must directly or indirectly instruct the new use in order to establish inducement. Similarly, where the patent claims the use of a combination, the PM must direct the infringer to use the combination in order to establish inducement.

[267] In this case, the claims are directed to a dosing regimen. While none of the cases cited above involved claims for a dosing regimen, in my view, a dosing regimen is analogous to a combination therapy in that dosage amounts and timing of doses must be combined to reach the claimed invention. Indeed, the Court has previously considered a cyclical dosage regimen to be a combination invention (*Procter & Gamble Pharmaceuticals Canada Inc v Canada (Minister of Health)*, 2004 FC 204 at para 26).

[268] The test for inducing infringement is well-established, and a finding of inducement requires the application of the tripartite test set out in *Corlac* at paragraph 162:

> i. The act of infringement must have been completed by the direct infringer;
>
> ii. The completion of the acts of infringement must be influenced by the acts of the alleged inducer to the point that, without the influence, direct infringement would not take place;
>
> iii.The influence must knowingly be exercised by the inducer, that is, the inducer knows that this influence will result in the completion of the act of infringement.

[269] Janssen submits that Teva will induce infringement of all three claim sets if it comes to market with its paliperidone palmitate product.

(1) The act of infringement must have been completed by the direct infringer

[270] While Teva argues that Janssen has no evidence that there will be any actual infringement and speculation cannot establish infringement, the combination of the IMS data for INVEGA SUSTENNA, the pharmacists' evidence that the Teva product will likely be interchangeable with INVEGA SUSTENNA, and the expert evidence of prescribing physicians is sufficient to establish that at least some patients will receive doses of the Teva paliperidone palmitate product corresponding to the claimed dosing regimens of 150 mg-eq on day 1, 100 mg-eq on day 8, and 75 mg-eq monthly thereafter for non-renally impaired patients, and 100 mg-eq on day 1, 75 mg-eq on day 8, and 50 mg-eq monthly thereafter for patients with renal impairment.

[271] While the IMS data and the evidence of Dr. Allain indicate that a large number of patients on INVEGA SUSTENNA receive 100 mg-eq or 150 mg-eq as their maintenance dose, Dr. Agid opined that many of his patients receive maintenance doses of 75 mg-eq. Dr. Simm acknowledged on cross-examination that he has treated at least some patients with INVEGA SUSTENNA using the claimed regimen of 150 mg-eq on day 1 in the deltoid, 100 mg-eq on day 8 in the deltoid, and 75 mg-eq as an ongoing maintenance dose. Dr. Simm stated that it is very likely that at least some patients will receive the Teva paliperidone product in accordance with the claimed dosing regimens in the 335 Patent for both renally impaired and non-renally impaired patients.

[272] Therefore, while acts of infringement may be few and far between, at least some physicians will prescribe and administer paliperidone palmitate injections that fall within the scope of the claimed dosing regimens in the 335 Patent.

(2) The completion of the acts of infringement must be influenced by the acts of the alleged inducer to the point that, without the influence, direct infringement would not take place

[273] This is the key aspect of the inducement analysis. [redacted]

[274] Janssen submits that the threshold to prove inducement on the basis of the PM is not high, and in any event, this is not a case where resort to "subtle references" in the PM is required. In Janssen's submission, the Teva PM goes beyond mere encouragement, and contains clear and explicit instructions that the Teva product is approved to be used in an infringing manner.

[275] I agree with Janssen that the Teva PM makes more than just a subtle reference to the infringing dosing regimen. Indeed, the 75 mg-eq maintenance dose is one of the "recommended" maintenance doses for non-renally impaired schizophrenia patients. [redacted]

[redacted]

[276] The jurisprudence is consistent that the PM is a key document in the inducement analysis, and the entire PM is to be considered (*Aventis Pharma*, above, at paras 51-52). With respect to the recommended dosing regimen, the "Dosage and Administration" section of the Teva PM is pertinent. The recommended dosing regimen for adult patients with schizophrenia or schizoaffective disorder is found on pages 30 and 31:

[277] [redacted]

[278] Teva's experts gave evidence that prescribing physicians do not look at generic PMs once they are sufficiently familiar with PMs and subsequent use of the brand products. [redacted]

[redacted]

[279] The recommended dosing regimen for patients with renal impairment is found under the "Dosage Adjustments for Special Populations" heading on page 34 of the Teva PM:

[redacted]

[280] [redacted]

[281] [redacted]

[282] Reading the sentence as a whole, I agree with Dr. Allain that as with the maintenance doses for non-renally impaired patients, the Teva PM recommends that the prescribing physician

select the maintenance dose for patients with renal impairment based on individual patient characteristics.

[283] Considering that the acts of infringement must be influenced by Teva to the point that, without the influence, direct infringement would not take place, Janssen's argument for inducement of infringement of all claims of the 335 Patent must fail.

[284] Drs. Simm and Allain both gave evidence that physicians do not consult generic PMs when they are sufficiently familiar with prescribing the brand product. For Dr. Allain's patients, she typically prescribes a maintenance dose of 100 to 150 mg-eq. Similarly, Dr. Simm stated that in his experience, the appropriate maintenance dose is determined individually for each patient, and in most cases the starting maintenance dose is 100 mg-eq. Drs. Simm and Allain both opined that physicians will consider the following factors when determining the appropriate maintenance dose for a given patient:

- The patient's response to prior depot or oral antipsychotics;
- Whether the patient's symptoms are well controlled;
- The side effects experienced by the patient;
- The age and physical health of the patient.

[285] Teva's experts' evidence is consistent that physicians prescribing maintenance doses of paliperidone palmitate will not be influenced by the Teva PM. This evidence is also consistent with statements made by Janssen in a document submitted to Health Canada that "[g]ood clinical practice is to individualize treatment based upon clinical symptoms" and "[i]ndividualization of

the dose of paliperidone palmitate can begin as early as day 36, the time corresponding to the third injection."

[286] Of the physicians, Dr. Agid was the outlier with respect to prescribing practices, opining that physicians slavishly follow the PM. At this point, INVEGA SUSTENNA has been on the market for over ten years, and psychiatric medical professionals are very familiar with using it in their practice. I do not accept that physicians will eschew good clinical practice in favour of a general recommendation in a PM.

[287] [redacted] The evidence in this case is that the maintenance dose truly does depend on individual patient characteristics such as age, weight, and tolerance of antipsychotics.

[288] Janssen highlights that the Teva PM will be instrumental in having the Teva paliperidone product added to hospital formularies. Be that as it may, the preferred expert evidence is that the PM itself does not actually result in prescription and use of the 75 mg-eq maintenance dose of paliperidone palmitate.

[289] Considering the totality of the evidence, particularly the evidence of Drs. Simm, Allain, and Virani that physicians and pharmacists must consider individual patient characteristics when prescribing and dispensing depot formulations of paliperidone palmitate rather than blindly following a number in a PM, I am not satisfied that the Teva PM influences physicians to

prescribe the claimed maintenance doses to the point that, absent the dosing information in the Teva PM, direct infringement would not occur.

[290] Based on this finding, consideration of the third part of the *Corlac* inducement test is unnecessary. Teva will not induce infringement of the 335 Patent if it comes to market with its paliperidone palmitate product. Teva must be aware that at least some infringement by third parties will occur, but this infringement is the result of prescribing physicians' skill and judgment applied to specific patient characteristics, rather than influence exercised by Teva via its PM.

IX. Conclusion

[291] In conclusion, Teva has not established that any of the Asserted Claims are invalid for obviousness. Janssen has satisfied the Court that Teva will directly infringe claims 1 to 16 and 33 to 48 of the 335 Patent if it comes to market with its paliperidone palmitate product.

X. Costs

[292] Pursuant to section 6.12 of the *Regulations*, the Court may make any order in respect of costs in accordance with the *Federal Courts Rules*, SOR/98-106. Amongst other factors, the Court may consider the diligence with which the parties have pursued the action and the extent to which they have reasonably cooperated in expediting the action.

[293] The Court notes that the parties cooperated commendably when a key witness fell ill in the weeks leading up to the initial trial date, working with the Court to reschedule the trial a few short months later and extend the statutory stay accordingly. This was no small task given the volume of evidence and the number of witnesses, and counsel's efforts on both sides are appreciated.

[294] The parties agreed that the successful party should be entitled to costs assessed as 35% of actual fees plus all disbursements, subject to representations on the reasonableness of the total actual fees and disbursements.

[295] Accordingly, Janssen is entitled to 35% of its actual legal fees plus 100% of disbursements.

JUDGMENT in T-353-18

THIS COURT'S JUDGMENT is that

1. The Asserted Claims are not obvious, and are valid.
2. The making, constructing, using, or selling of Teva-Paliperidone Injection prolonged release injectable suspensions of paliperidone palmitate by Teva in accordance with ANDS No. 210095 would directly infringe claims 1 to 16 and 33 to 48 of the 335 Patent. Teva will not directly infringe claims 17 to 32, and will not induce infringement of any of the Asserted Claims.
3. An injunction is granted until the expiry of the 335 Patent on December 17, 2028, restraining Teva 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 Teva-Paliperidone Injection in Canada in accordance with ANDS No. 210095;
   b. offering for sale, marketing or having Teva-Paliperidone Injection marketed in Canada in accordance with ANDS No. 210095; and
   c. importing, exporting, distributing or having Teva-Paliperidone Injection distributed in Canada in accordance with ANDS No. 210095.
4. Costs to Janssen assessed as 35% of its actual legal fees plus 100% of disbursements.

"Michael D. Manson"
Judge

FEDERAL COURT

SOLICITORS OF RECORD

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