Federal Court Cour fédérale

**Date: 20240326**

**Docket: T-1007-20**

**Citation: 2024 FC 424**

**Toronto, Ontario, March 26, 2024**

**PRESENT: Madam Justice Pallotta**

**BETWEEN:**

**MEDEXUS PHARMACEUTICALS INC., MEDEXUS INC. and MEDAC GESELLSCHAFT FÜR KLINISCHE SPEZIALPRÄPARATE MBH**

**Plaintiffs (Defendants by Counterclaim)**

**and**

**ACCORD HEALTHCARE INC. AND INTAS PHARMACEUTICALS LTD.**

**Defendants (Plaintiffs by Counterclaim)**

**PUBLIC JUDGMENT AND REASONS**

**(Identical to the Confidential Judgment and Reasons issued on March 14, 2024)**

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## I. **Introduction**

[1] In this patent action the plaintiffs seek remedies for the defendants' alleged infringement of Canadian Patent No 2,659,662 titled "Concentrated Methotrexate Solutions" (662 Patent). The opening paragraph of the 662 Patent states:

> The present invention relates to concentrated methotrexate solutions. In particular, the present invention relates to the use of methotrexate in the production of a parenterally administered medicament for the treatment of inflammatory autoimmune diseases, wherein the methotrexate is present in a pharmaceutically acceptable solvent at a concentration of more than 25 mg/ml. The invention also relates to a ready-made syringe and a carpule containing such a pharmaceutical solution formulation, as well as a pen injector comprising such a carpule and/or a ready-made syringe.

[2] The plaintiff medac Gesellschaft für klinische Spezialpräparate mbH (medac), owner of the 662 Patent, manufactures Metoject® pre-filled (or ready-made) syringes containing a 50 mg/ml methotrexate solution for parenteral administration. Specifically, Metoject® syringes are approved for subcutaneous injection and can be prescribed to treat severe disabling rheumatoid arthritis and psoriasis/psoriatic arthritis, which are inflammatory autoimmune diseases (IADs). Rheumatoid arthritis mainly affects synovial joints. Psoriasis mainly affects the skin and can develop into psoriatic arthritis.

[3] Metoject® syringes are offered as 7.5, 10, 12.5, 15, 17.5, 20, 22.5 and 25 mg doses of methotrexate. For example, a 10 mg dose syringe would contain 0.2 ml of a 50 mg/ml methotrexate solution for injection and a 25 mg dose syringe would contain 0.5 ml of a 50 mg/ml methotrexate solution for injection.

[4] The plaintiffs Medexus Inc and Medexus Pharmaceuticals Inc claim relief as licensees of the 662 Patent. Medexus Inc marketed Metoject® products in Canada until it merged with Medexus Pharmaceuticals Inc in 2021. Since then, medac has licensed Medexus Pharmaceuticals Inc to market and sell Metoject® products in Canada.

[5] The defendant Accord Healthcare Inc (Accord), a subsidiary of Intas Pharmaceuticals Ltd (Intas), received Health Canada approval to market methotrexate products for subcutaneous injection based on a comparison to medac's Metoject® products. Accord received approval to market syringes pre-filled with a 50 mg/ml methotrexate solution in 2019 (Accord Products), and it received approval to market injector devices pre-filled with a 50 mg/ml methotrexate solution in 2022 (Methofill Products). Intas is the manufacturer of these products.

## II. **Issues and Determinative Issue**

[6] The plaintiffs assert that the defendants infringe claims 1 to 10, 18 to 22, 35, and 39 of the 662 Patent (Asserted Claims), including by importing and selling Accord Products and Methofill Products in Canada.

[7] The defendants contend they are not liable for patent infringement because each of the Asserted Claims is invalid. The defendants allege that the subject matter of the Asserted Claims is not inventive and that medac has claimed a monopoly for what amounts to an obvious extension of its existing methotrexate product line. The defendants also allege that some or all of the Asserted Claims are invalid because their subject matter was anticipated, insufficiently disclosed, overbroad, or ambiguous, or because utility was not supported across the full scope of

the claim. The defendants counterclaim for a declaration that the 662 Patent claims are, and always have been, invalid and of no force or effect.

[8] Just before the commencement of trial, the defendants conceded that the Accord Products and the Methofill Products would infringe the Asserted Claims if they are valid. As a result of the concession, the plaintiffs did not lead evidence to establish that the Accord Products and Methofill Products fall within the scope of the Asserted Claims. There are no non-infringement issues before the Court, apart from validity.

[9] Consequently, the issues in this action relate to claim construction, validity, and the remedy for infringement of any valid Asserted Claims.

[10] The only point of claim construction in dispute relates to the meaning of the term ‘about 50 mg/ml’ in claims 3 and 20 of the 662 Patent.

[11] The defendants bear the onus of establishing that the Asserted Claims are invalid. They advance the following grounds of invalidity:

i. anticipation (claims 1-6);
ii. obviousness;
iii. ambiguity (claims 3, 20 and their dependent claims);
iv. lack of demonstrated or soundly predicted utility across the full scope of the claims;
v. insufficiency; and
vi. overbreadth.

[12] Schedule A to these reasons is a list of scientific references the parties relied on, including 22 references the defendants pleaded as prior art. Where I refer to a reference in these reasons, I use the short form notation identified in bold text in Schedule A.

[13] If the defendants infringe at least one valid Asserted Claim, the plaintiffs ask the Court to award monetary relief for past infringement and an injunction to prevent future infringement. With respect to monetary relief, the plaintiffs elected damages instead of an accounting of the defendants' profits. The plaintiffs seek an award of damages to compensate them for lost Metoject® profits resulting from the defendants' sales of infringing products.

[14] For the reasons below, the Asserted Claims are invalid for obviousness. Obviousness is the determinative issue in the action and the defence fully succeeds on this basis.

[15] It is not necessary to address the other invalidity grounds. However, I will address the other invalidity grounds to the extent they relate to the narrowest Asserted Claim the defendants were required to invalidate to succeed in their defence. In view of the defendants' concession that they would infringe all Asserted Claims, no purpose would be served by deciding whether claims 1-6 are invalid for anticipation. Ambiguity affects the narrowest Asserted Claim. I will address ambiguity in detail because it overlaps with claim construction, and because two expert witnesses addressed it in some detail and were cross-examined at length on this ground. I will address utility, insufficiency, and overbreadth to the extent these grounds affect the narrowest Asserted Claim; however, the analysis is brief in view of my findings on obviousness.

## III. **Background on Methotrexate**

[16] Methotrexate has a long history of use as a medication—since about the 1950s.

[17] Methotrexate was first used to treat certain forms of cancer. It belongs to a class of chemotherapeutic agents known as antifolates, which inhibit cell proliferation by antagonizing folic acid and interfering with the synthesis of tetrahydrofolate. Tetrahydrofolate is involved in a variety of intracellular processes including the synthesis, repair, and replication of DNA.

[18] By the 1980s, clinical trials had established methotrexate's effectiveness in treating IADs—that is, diseases characterized by inflammation caused by the body's immune system attacking its own cells. Methotrexate soon became a standard treatment for rheumatoid arthritis, psoriasis, and other IADs.

[19] When used to treat IADs, methotrexate is prescribed at lower doses than those typically used for cancer treatment. At lower doses methotrexate acts as an immunosuppressant, but even today, its mechanism of action in this regard is not fully understood. At the doses used to treat IADs, methotrexate is classified as a disease modifying anti-rheumatic drug (DMARD). DMARDs modify the body's inflammatory response in a different way than steroids or non-steroidal anti-inflammatory drugs. DMARDs can slow the progression of the disease.

[20] Patients on methotrexate for IADs typically remain on methotrexate indefinitely, taking the drug weekly in the form of orally administered tablets or injections of a solution containing the prescribed dose.

## IV. **662 Patent and Asserted Claims**

[21] The 662 Patent was filed in Canada on July 20, 2007 with an earlier claimed priority filing date based on a German patent application filed on July 21, 2006. The application for the 662 Patent was published on January 24, 2008. The 662 Patent issued on January 20, 2015.

[22] As noted above, the 662 Patent specification states the invention relates to concentrated methotrexate solutions, and in particular, the use of methotrexate in the production of a parenterally administered medicament for the treatment of IADs wherein the methotrexate is present in a pharmaceutically acceptable solvent at a concentration of more than 25 mg/ml. In an especially preferred embodiment, the methotrexate is present in a pharmaceutically acceptable solvent at a concentration of about 50 mg/ml.

[23] Parenteral administration refers to routes of administration that avoid the gastrointestinal tract. While the 662 Patent does not define 'parenteral', it states the medicament is administered by intravenous, intramuscular, or subcutaneous injection. Subcutaneous administration is an injection into the tissue immediately below the skin. A preferred embodiment of the 662 Patent provides that the methotrexate solution is in a form suitable for subcutaneous self-administration by the patient and all Asserted Claims include a limitation of subcutaneous administration.

[24] The 662 Patent specification states the medicaments of the invention are directed to the treatment of all IADs that can reasonably be treated with methotrexate; for example, rheumatoid arthritis, juvenile arthritides, vasculitides, collagenoses, Crohn's disease, colitis ulcerosa, bronchial asthma, Alzheimer's disease, multiple sclerosis, Bechterew's disease, joint arthroses or psoriasis, as well as psoriasis arthritis and in particular plaque-type psoriasis vulgaris. The

specification states the medicaments are especially preferred for the treatment of rheumatoid arthritis, including juvenile arthritides, such as specifically the oligoarthritic and polyarthritic forms of juvenile arthritis.

[25] The Asserted Claims are independent claims 1 and 18 and dependent claims 2-10, 19-22, 35, and 39, as they directly or indirectly depend from one another. The same Asserted Claims are advanced against the Accord Products and the Methofill Products.

[26] Claim 1 relates to the use of methotrexate to produce a subcutaneously administered medicament for the treatment of IADs where the methotrexate is present in a solvent at a concentration greater than 30 mg/ml. Claim 18 relates to a ready-made syringe comprising a methotrexate formulation for subcutaneous administration where the concentration of methotrexate is greater than 30 mg/ml. The dependent claims add limitations on methotrexate concentration, methotrexate dosage, the solvent, disease indications, and/or aspects of administration.

[27] The Asserted Claims in the 662 Patent read as follows (independent claims are shown in bold text):

> **1. Use of methotrexate for the production of a subcutaneously administered medicament for the treatment of inflammatory autoimmune diseases, wherein the methotrexate is present in a pharmaceutically acceptable solvent at a concentration of more than 30 mg/ml.**
>
> 2. Use according to claim 1, wherein the methotrexate is present at a concentration of more than 30 mg/ml to 100 mg/ml.
>
> 3. Use according to claim 2, wherein the methotrexate is present at a concentration of about 50 mg/ml.

4. Use according to any one of claims 1 to 3, wherein the pharmaceutically acceptable solvent is selected from water, water for injection purposes, water comprising isotonization additives and sodium chloride solution.

5. Use according to any one of claims 1 to 4, wherein the inflammatory autoimmune disease is selected from rheumatoid arthritis, juvenile arthritides, vasculitides, collagenoses, Crohn's disease, colitis ulcerosa, bronchial asthma, Alzheimer's disease, multiple sclerosis, Bechterew's disease, joint arthroses, or psoriasis.

6. Use according to claim 5, wherein the inflammatory autoimmune disease is rheumatoid arthritis.

7. Use according to any one of claims 1 to 6, wherein the medicament is present in a form suitable for patient self-administration.

8. Use according to any one of claims 1 to 7, wherein the medicament is contained in an injection device for a single application.

9. Use according to claim 8, wherein the injection device contains a dosage of 5 to 40 mg.

10. Use according to claim 8 or 9, wherein the injection device is a ready-made syringe.

…

**18. Ready-made syringe, comprising a pharmaceutical solution formulation of methotrexate with a concentration of more than 30 mg/ml in a pharmaceutically acceptable solvent for subcutaneous administration.**

19. Ready-made syringe according to claim 18, wherein the methotrexate is present at a concentration of more than 30 mg/ml to 100 mg/ml.

20. Ready-made syringe according to claim 19, wherein the methotrexate is present at a concentration of about 50 mg/ml.

21. Ready-made syringe according to any one of claims 18 to 20, comprising a dosage of 5 to 40 mg.

22. Ready-made syringe according to any one of claims 18 to 21, wherein the pharmaceutically acceptable solvent is selected from

> water, water for injection purposes, water comprising isotonization additives and sodium chloride solution.
>
> …
>
> 35. Use according to claim 9, wherein the injection device contains a dosage of 5.0, 7.5, 10.0, 12.5, 15.0, 17.5, 20.0, 22.5, 25.0, 27.5, 30.0, 32.5, 35.0, 37.5 or 40.0 mg, of methotrexate.
>
> …
>
> 39. Ready-made syringe according to claim 21, comprising a dosage of 5.0, 7.5, 10.0, 12.5, 15.0, 17.5, 20.0, 22.5, 25.0, 27.5, 30.0, 32.5, 35.0, 37.5 or 40.0 mg, of methotrexate.

## V. **Evidence**

[28] The parties agreed on many facts. They provided a joint scientific primer and a joint statement of facts.

[29] The parties introduced expert evidence in support of their respective positions on claim construction and validity. The plaintiffs had served a report by an expert witness who opined on claim construction and infringement, but they elected not to call that witness at trial in view of the defendants' concession on infringement. For the same reason, the defendants did not rely on a report by one of its experts, Peter Rue, on the issue of infringement. While it is often the case that a defendant will lead evidence first when validity is the main issue for determination, the trial schedule was set before the defendants withdrew their non-infringement defence and the plaintiffs led their evidence first.

[30] The plaintiffs called three expert witnesses: Elena Massarotti, Patrick J Sinko, and Andrew Harington. The plaintiffs also called three fact witnesses: the inventor Heiner Will, as well as Mark Jansen and Matthijs Janssen, who are authors of a prior art reference the defendants

rely on. The defendants raised evidentiary objections to the testimony of Drs. Jansen and Janssen, arguing their testimony is irrelevant, improper, and prejudicial because it was expert opinion rather than fact evidence.

[31] The defendants called two expert witnesses: Johannes Roth and Peter Rue. They did not call an expert witness on damages.

[32] The following provides an overview of each side's witnesses and their evidence.

A. *Dr. Massarotti (plaintiffs' expert witness)*

[33] Dr. Massarotti is a rheumatologist, professor, and researcher. Dr. Massarotti received her MD from Tufts University School of Medicine in 1984 and completed her internship and residency in internal medicine at New England Medical Center (which later became Tufts Medical Center) from 1984 to 1987. From 1988 to 1990, Dr. Massarotti completed a fellowship in Rheumatology/Immunology at New England Medical Center, and from 1990 to 1991 she was the Chief Medical Resident. Dr. Massarotti held several positions related to rheumatology at Tufts Medical Center between 1993 and 2007, including director of clinical rheumatology training, acting division chief of rheumatology, and clinical director of rheumatology.

[34] Dr. Massarotti is board certified in internal medicine and in rheumatology and a member of the American College of Rheumatology. She is an Associate Professor at Harvard Medical School and an Associate Physician at Brigham and Women's Hospital. At the hospital, Dr. Massarotti is the director of clinical trials for the Lupus Center and a co-director of the Clinical Trials Center at the Division of Rheumatology. Dr. Massarotti is active in academia, serving as

an *ad hoc* reviewer for several medical journals, serving on the executive committee of the Lupus Nephritis Trials Network, and publishing peer-reviewed articles, review articles, book chapters, and abstracts, including reports of clinical trials, epidemiologic studies, and clinical observations in the areas of autoimmune disease.

[35] The plaintiffs proposed that Dr. Massarotti was qualified to provide expert opinion evidence as:

> A physician, associate professor of medicine, and clinical researcher with expertise in (1) rheumatology, (2) the treatment of patients suffering from inflammatory autoimmune diseases with methotrexate, and (3) the analysis and interpretation of experimental results, including from pre-clinical and clinical trials in clinical rheumatology, in the area of inflammatory autoimmune diseases, including rheumatoid arthritis.

[36] The defendants did not object to Dr. Massarotti's proposed qualifications and I was satisfied she was qualified to provide expert opinion evidence according to the plaintiffs' proposed qualifications.

[37] Dr. Massarotti's expert report dated September 8, 2022 sets out her opinions on specific mandates related to the qualifications and knowledge of the skilled person, construction of the Asserted Claims, and the validity of the Asserted Claims. Confidential and public versions of her report were marked as trial exhibits. Her report was taken as read.

B. *Dr. Sinko (plaintiffs' expert witness)*

[38] Dr. Sinko is a pharmaceutical consultant, registered pharmacist, professor, and researcher. Dr. Sinko earned a Bachelor of Science degree in pharmacy from the College of Pharmacy, Rutgers University in 1982 and he received a PhD in pharmaceutics from the College

of Pharmacy, University of Michigan in 1988. From 1988 to 1991, Dr. Sinko was a Research Scientist at the University of Michigan and Therapeutic Systems Research Labs. Dr. Sinko has been a Professor in the Department of Pharmaceutics at Rutgers University's College of Pharmacy since 1991 and was appointed Distinguished Professor in 2007. Dr. Sinko has held several positions in academic publishing, including a current position as Editor-in-Chief (Biopharmaceutics) for the journal *Pharmaceutics* and a previous position as Section Editor for the *European Journal of Pharmaceutical Sciences*.

[39] Dr. Sinko is a member of the American Association for the Advancement of Science, American Association of Pharmaceutical Scientists, American Association of Colleges of Pharmacy, American College of Clinical Pharmacy, American Diabetes Association, American Society of Microbiology, and the Controlled Release Society. In 2003, he was elected as a fellow of the American Association of Pharmaceutical Scientists for being internationally recognized as an expert in biopharmaceutics and drug delivery.

[40] Dr. Sinko has authored, edited, and published articles in scientific journals, books, and chapters, including publications relating to injectable formulations. He has consulted for pharmaceutical and biotechnology companies and he has experience formulating injectable dosage forms including intradermal, subcutaneous, and intramuscular injections.

[41] The plaintiffs proposed that Dr. Sinko was qualified to provide expert opinion evidence as:

> A professor, researcher, and registered pharmacist with expertise in (1) pharmaceutical science and formulation, including first-hand experience with a wide range of drugs and dosage forms, including

> the use of methotrexate, and (2) formulating drug delivery systems, including for subcutaneous, intramuscular, and intravenous injectable dosage forms.

[42] The defendants did not object to Dr. Sinko's proposed qualifications and I was satisfied he was qualified to provide expert opinion evidence according to the plaintiffs' proposed qualifications.

[43] Dr. Sinko's expert report dated September 9, 2022 sets out his opinions on the qualifications and knowledge of the skilled person, construction of the Asserted Claims, and the validity of the Asserted Claims. Confidential and public versions of Dr. Sinko's report were marked as trial exhibits. His report was taken as read.

C. *Mr. Harington (plaintiffs' expert witness)*

[44] Mr. Harington is a Chartered Professional Accountant, Chartered Financial Analyst charterholder, and Chartered Business Valuator. Mr. Harington earned a Bachelor of Commerce degree from the University of Cape Town in 1991, as well as a Bachelor of Commerce (Honours) degree in Financial Accounting and a Post Graduate Diploma in Accounting from the University of Cape Town in 1992. In South Africa, Mr. Harington was registered as a Chartered Accountant in 1995. In Canada, he was registered as a Chartered Accountant in 1998, a Chartered Financial Analyst in 2002, and a Chartered Business Valuator in 2005. Currently, Mr. Harington is a principal at The Brattle Group. Mr. Harington has experience in the valuation of businesses, intellectual property, and financial damages quantification. He has prepared investigative accounting and damage quantification reports for proceedings in the Federal Court and Ontario Superior Court.

[45] Mr. Harington is the lead author of the 2018 edition of *Calculating Monetary Remedies in Intellectual Property Cases in Canada – a Reference Book of Principles and Case Law*. He co-authored two earlier monographs published in 2012: *Damages Calculations in Intellectual Property Cases in Canada* and *Accounting of Profits Calculations in Intellectual Property Cases in Canada*.

[46] The plaintiffs proposed that Mr. Harington was qualified to provide expert opinion evidence as:

> A Chartered Professional Accountant, Chartered Financial Analyst charterholder, and Chartered Business Valuator who is qualified to provide expert evidence on investigative and forensic accounting, business valuation, and quantification of financial remedies, including accounting of profits in patent infringement disputes.

[47] The defendants did not object to Mr. Harington's proposed qualifications. I was satisfied he was qualified to provide expert opinion evidence according to the plaintiffs' proposed qualifications.

[48] Mr. Harington's June 10, 2022 expert report sets out his opinions on quantifying the plaintiffs' lost profits due to the defendants' sales. Significant parts of Mr. Harington's report refer to solicitor's eyes only (SEO) confidential information. SEO confidential and public versions of Mr. Harington's report were marked as trial exhibits. His report was taken as read.

D. *Mr. Will (plaintiffs' fact witness)*

[49] Mr. Will is the sole inventor named in the 662 Patent. He has been employed at medac since 1984 and he was managing director of medac's autoimmune group at the material times. Mr. Will testified about his roles at medac, the invention story, his role in the development of the

Metoject® product, and medac's business relationships regarding the product. He introduced a number of exhibits including medac documents that are written in German. Documents in the German language were entered as a three-part trial exhibit comprising the German document, the English translation of the document, and the translator's affidavit. There was a pre-trial process for exchanging and raising any issue with certified translations of German documents and neither party raised an issue with the English translations of documents that were marked as trial exhibits.

[50] Although Mr. Will's first language is German, he speaks English well. The parties agreed to have a German translator present throughout Mr. Will's testimony in chief and cross-examination to provide assistance when needed. Mr. Will requested assistance from the interpreter from time to time, but for the most part Mr. Will testified capably in English.

E. *Dr. Mark Jansen and Dr. Matthijs Janssen (plaintiffs' fact witnesses)*

[51] Dr. Mark Jansen is a hospital pharmacist and clinical pharmacologist. Dr. Matthijs Janssen is a retired rheumatologist.

[52] Drs. Jansen and Janssen were working in their respective fields before 2006 and they are co-authors (together with a third author, Elsbeth Nagtegaal) of an academic article published in the scientific journal *Pharmaceutisch Weekblad* in 1999. The article is titled (translation) "Intramuscular and subcutaneous administration in rheumatoid arthritis, Methotrexate outside the clinic" and discusses intramuscular or subcutaneous injection as an alternative to oral methotrexate in the treatment of inflammatory autoimmune diseases. Jansen 1999 is one of the references discussed in the expert reports and there is no dispute that it is a prior art reference

that could have been located by the skilled person. The original Dutch article was entered as a trial exhibit together with an English translation and translator's certificate.

[53] The defendants brought a motion to exclude Drs. Jansen and Janssen from testifying on the basis that their evidence would be inadmissible. I declined to rule on admissibility before hearing the evidence.

[54] Drs. Jansen and Janssen each testified about the Jansen 1999 article, as well as their personal knowledge and experience relating to the preparation and use of methotrexate solutions at the material times. The latter included evidence about aspects of the state of the art, as well as answers to questions asking whether Drs. Jansen and Janssen had considered increasing the concentration of methotrexate solutions or creating a new methotrexate formulation.

[55] My admissibility ruling is in the next section of these reasons.

F. *Dr. Roth (defendants' expert witness)*

[56] Dr. Roth is a pediatric rheumatologist, professor, and researcher. Dr. Roth received his MD from the University of Tuebingen in 1996 and then completed a residency in pediatrics and a fellowship in pediatric rheumatology. From 2001 to 2007, Dr. Roth practiced as an academic pediatric rheumatologist at Charité University and completed his habilitation, which is an extended PhD thesis under the German academic system. Since 2007, Dr. Roth has been Chief of the Division of Pediatric Dermatology and Rheumatology at the Children's Hospital of Eastern Ontario and a professor of pediatrics at the University of Ottawa's Faculty of Medicine.

[57] Dr. Roth's clinical practice includes diagnosis, treatment, and management of patients. While his clinical practice is focussed on pediatric rheumatic diseases, he also treats adult patients over the age of 18 when they have not yet been transitioned to a rheumatologist who treats adult patients.

[58] Dr. Roth is active in academia, having published numerous peer-reviewed papers, abstracts, and book chapters primarily in the field of pediatric rheumatology. Dr. Roth has acted as both a principal investigator and co-investigator in clinical trials, including trials related to rheumatology.

[59] The plaintiffs did not object to Dr. Roth's proposed qualifications. I was satisfied Dr. Roth was qualified to provide expert opinion evidence according to the proposed qualifications that were put forward by the defendants:

> Dr. Johannes Roth is an academic and clinical pediatric rheumatologist who has expertise in the diagnosis, treatment, and management of autoimmune disorders including in particular both juvenile and adult rheumatic diseases such as rheumatoid arthritis and juvenile idiopathic arthritis. Dr. Roth also has expertise in the prescribing, dosing, and administration of methotrexate to patients.

[60] Dr. Roth prepared an expert report dated June 10, 2022. The report sets out Dr. Roth's opinions on a number of specific mandates related to the qualifications and knowledge of the skilled person, construction of the Asserted Claims, and the validity of the Asserted Claims. Confidential and public versions of Dr. Roth's report were marked as trial exhibits and taken as read.

G. *Dr. Rue (defendants' expert witness)*

[61] Dr. Rue is a pharmaceutical consultant. Dr. Rue earned a Bachelor of Science degree in 1973 and a PhD in pharmacy in 1978 from the University of Aston in Birmingham. He worked in the Formulation Development Department of the Beecham Pharmaceuticals Research Division of Burgh Heath from 1977 to 1980. Dr. Rue was employed at the Pharmaceutical Research Department of Glaxo Group Research of Ware, England from 1980 to 1995 and headed the Pharmaceutical Development Department from 1990 to 1995. Dr. Rue was a visiting professor at the University of Aston from 2001 to 2017, teaching solid dosage form modules as part of the Masters program in pharmacy.

[62] Dr. Rue is a member of the Royal Pharmaceutical Society of Great Britain. He has co-authored academic publications, including publications related to pharmaceutical formulations and compositions, and is a named inventor on a number of pharmaceutical patents.

[63] The plaintiffs did not object to Dr. Rue's proposed qualifications. I was satisfied Dr. Rue was qualified to provide expert opinion evidence according to the proposed qualifications that were put forward by the defendants:

> Dr. Peter J. Rue is a pharmaceutical consultant who has expertise in drug development, pharmaceutical formulation, and drug delivery, including in the design and development of liquid pharmaceutical formulations and injectable pharmaceutical formulations.

[64] Dr. Rue prepared an expert report dated June 1, 2022. The report sets out Dr. Rue's opinions on mandates related to the qualifications and knowledge of the skilled person, construction of the Asserted Claims, and the validity of the Asserted Claims.

[65] The defendants had served a second expert report from Dr. Rue, on infringement. In view of their concession on infringement, the defendants did not rely on Dr. Rue's second report.

[66] The defendants sought leave to introduce a third expert report from Dr. Rue dated October 26, 2022, to reply to Dr. Sinko's expert opinion on the issue of ambiguity. In a decision dated December 14, 2022 (2022 FC 1734), I granted the motion in part. At trial, the defendants tendered a redacted copy of Dr. Rue's third report that only included the paragraphs I had found to be proper reply evidence, namely, paragraphs 1-4, 6-8, 10-11, the first sentence of paragraph 12, paragraphs 16-22, and the first sentence of paragraph 23.

[67] Confidential and public versions of Dr. Rue's first report, as well as the redacted copy of his third report (which did not contain any confidential information), were marked as trial exhibits and taken as read.

## VI. **Admissibility of Dr. Jansen's and Dr. Janssen's Testimony**

[68] On the first day of trial, the defendants brought a motion to exclude Drs. Jansen and Janssen from testifying, on grounds that their testimony would be irrelevant, improper, and prejudicial. The defendants argued the proposed testimony would be irrelevant because Drs. Jansen and Janssen were being put forward to testify about their personal knowledge and experience with methotrexate, but the question of obviousness is an objective assessment based on expert evidence of the skilled person's perspective and assessment of the prior art. The defendants also argued the proposed testimony would be improper and prejudicial because it would be tantamount to expert opinion tendered under the guise of fact evidence, without complying with procedural safeguards for opinion evidence. They noted that Drs. Jansen and

Janssen have expertise similar to that of the experts in this case and would be testifying about issues addressed in the experts' reports. The defendants argued the proposed testimony would prejudice the Court's fact finding process as it would overlap with the parties' expert evidence and render it impossible to extricate determinations properly made on the expert evidence from those improperly made based on Dr. Jansen's or Dr. Janssen's testimony.

[69] In response, the plaintiffs argued that the evidence: (i) should be judged by its content (*Dow Chemical Canada ULC v Nova Chemicals Corporation*, 2015 ABQB 401 at para 25) as fact evidence within Dr. Jansen's and Dr. Janssen's personal knowledge and experience, and not judged by whether these witnesses have the same expertise as the experts or would give testimony that relates to issues addressed in the expert reports; (ii) would be relevant as testimony from an actual person of ordinary skill that would help to resolve conflicting expert evidence on obviousness (*Windsurfing International Inc v Trilantic Corp* (1985), 8 CPR (3d) 241 at 259-260, 35 ACWS (2d) 255 (FCA); *Merck & Co Inc v Apotex Inc,* 2005 FC 755 at para 73); and (iii) being relevant and material, should only be excluded if its prejudicial effect on the fairness and integrity of the proceeding outweighs its value (*R v Collins* (2001), 160 CCC (3d) 85, 2001 CanLII 24124 at para 19 (ONCA)).

[70] After considering both sides' arguments, I dismissed the defendants' motion to exclude Drs. Jansen and Janssen from testifying. I was not satisfied, based solely on the short descriptions of proposed testimony set out in will-say statements, that the evidence or parts of it would be inadmissible. I decided that admissibility was something I would need to determine after hearing the testimony or at least after hearing enough of it to make a ruling.

[71] I refused to direct, as the plaintiffs had requested, that Dr. Jansen's and Dr. Janssen's testimony be admitted as long as it was limited to facts within their personal knowledge as set out in the will-say statements. I held that admissibility was not simply a question of whether these witnesses stayed within the proposed testimony set out in their will-say statements. While the will-say statements were a constraint, I held that evidence falling squarely within the will-say statements might be inadmissible as opinion evidence or for other reasons.

[72] The result was that I declined to rule on admissibility before hearing the evidence and I reserved my determination on admissibility.

[73] As a practical way to minimize the disruption of objections during Dr. Jansen's and Dr. Janssen's testimony, it was agreed that the defendants would be permitted to register a general objection on the grounds set out in their motion and defendants' counsel would only rise to object on a different ground (for example, a hearsay objection). I ruled on the additional objections from the bench.

[74] Turning to the general objection, I agree with the defendants that Dr. Jansen's and Dr. Janssen's testimony is inadmissible. Their testimony related to three general topics: (i) Jansen 1999; (ii) aspects of the state of the art; and (iii) whether these witnesses considered increasing the concentration of methotrexate solutions or creating a new methotrexate formulation.

[75] On the first topic, Drs. Jansen and Janssen testified about what they wrote in Jansen 1999. Sometimes the testimony strayed into an explanation of what they meant by certain statements in the article. Testimony repeating what was written in Jansen 1999 was unnecessary. Testimony

elaborating on Jansen 1999 was irrelevant—I agree with the defendants that what is relevant to the issues in this action is how the skilled person reading Jansen 1999 would have understood the article at the relevant time, not what the authors intended. That said, Dr. Jansen's and Dr. Janssen's testimony about Jansen 1999 was not materially different from the plain meaning of the article and the expert witnesses' opinions on what the skilled person would take from it. Therefore, practically speaking, nothing turns on whether these witnesses' evidence about Jansen 1999 is admissible or not.

[76] On the second topic, Dr. Jansen and/or Dr. Janssen testified about the dosage forms and concentrations of methotrexate that were used as of July 2006. They also testified about whether they or their colleagues drew on information or products from the treatment of cancer to inform how to treat patients with autoimmune diseases, and whether patients with rheumatoid arthritis would experience injection pain with subcutaneously administered methotrexate. In my view, this evidence is inadmissible as improper expert opinion. In any event, and regardless of how the evidence is characterized, I do not agree with the plaintiffs that the evidence assists to resolve any contentious aspects of the experts' evidence on the above points. Drs. Jansen and Janssen were not instructed on the proper framework, they did not approach these questions from the skilled person's perspective in light of the applicable legal principles, their evidence did not clearly favour or contradict any experts' opinion, and they did not provide sufficient explanation to assist the Court in resolving any contentious points about the state of the art or the common general knowledge.

[77] For similar reasons, I find Drs. Jansen's and Janssen's evidence in respect of the third topic to be inadmissible. They answered 'no' to a series of questions asking whether, as of July

21, 2006: (i) either of them had ever raised the concentration of methotrexate solutions above 25 mg/ml, had considered doing so, or had considered creating a new methotrexate formulation for subcutaneous administration to treat IADs; and (ii) anyone had suggested raising concentration above 25 mg/ml or whether they were aware of anyone else doing so. While the actions of an "actual" person of ordinary skill can be relevant to an obviousness analysis, the evidence of Drs. Jansen and Janssen is not relevant or helpful to the obviousness inquiry in this case. Their negative answers to the questions posed do not assist the Court to resolve any contentious points. Drs. Jansen and Janssen did not provide an explanation or context for their answers and their evidence did not contribute to the Court's understanding of the issues. It is also unclear what Drs. Jansen and Janssen meant by their answers, which did not favour either party and were equally consistent with the defendants' position and the defendants' experts' opinions that injection volume was not a big problem with the 25 mg/ml solution conventionally used for rheumatoid arthritis.

## VII. **Principles: Skilled Person and Common General Knowledge**

[78] The person of skill in the art is a legal construct embodying a number of concepts that inform a proper approach to resolving issues of claim construction, infringement, and validity in a patent action.

[79] For example, the skilled person possesses a level of skill and knowledge necessary to appreciate the nature and description of the invention at a technical level, and to put it into practice: *Whirlpool Corp v Camco Inc*, 2000 SCC 67 at para 53 [*Whirlpool*]. This is the ordinary level of skill and knowledge of the particular art or science to which the patent relates: *Free World Trust v Électro Santé Inc*, 2000 SCC 66 at para 44 [*Free World*]. The skilled person

embodies the common general knowledge (CGK) that is generally known and accepted in the field, and they are reasonably diligent in keeping up with advances: *Whirlpool* at para 74.

[80] Where a patent relates to multiple scientific or technical fields, the skilled person can comprise a team of people: *Allergan Inc v Apotex Inc*, 2022 FC 260 at para 146 [*Allergan*].

[81] The CGK consists of what the skilled person would generally know and accept at the relevant time: *Mylan Pharmaceuticals ULC v Eli Lilly Canada Inc*, 2016 FCA 119 at para 24 [*Mylan*], citing *Apotex Inc v Sanofi-Synthelabo Canada Inc*, 2008 SCC 61 at para 37 [*Sanofi*]. Information only migrates into the CGK if the skilled person would become aware of it and accept it as a good basis for further action: *Mylan* at para 24.

[82] In this case, the relevant time is as of January 24, 2008 for the claim construction analysis and as of July 21, 2006 for the obviousness analysis; however, all experts agree the CGK would be the same at any of the material dates for deciding the issues in this action. There is no difference between the CGK as of 2006 and as of 2008.

[83] The skilled person is not inventive. They pursue reasonable and logical enquiries and can make deductions based on the information available, but they possess no imagination or inventiveness: *Allergan* at para 149; *Beloit Canada Ltd v Valmet Oy* (1986), 8 CPR (3d) 289 at 294, [1986] FCJ No 87 (FCA) [*Beloit*].

[84] The skilled person also addresses each issue at the correct point in time. As noted above, the parties and experts in this case do not identify any material differences in the prior art or

CGK as of the various relevant dates, which simplifies the analysis. Nonetheless, the Court must guard against hindsight and the dangers of a backward-looking perspective: *Beloit* at 294.

[85] Expert witnesses assist the Court by opining on the qualifications, relevant experience, and knowledge of the notional skilled person, and how to assess the issues in dispute from the skilled person's frame of reference in view of the relevant experience and knowledge they bring to bear: *Tetra Tech EBA Inc v Georgetown Rail Equipment Company*, 2019 FCA 203 at para 88, citing *Free World* at para 51.

[86] The parties' arguments regarding the skilled person's attributes and CGK, along with my analysis, are found in the validity section of these reasons. This is because the parties' disagreements on these points do not affect their positions on claim construction, but do affect their positions on validity. While my analysis appears later in these reasons, I have considered all issues, including claim construction, from the perspective of the skilled person and having regard to the CGK.

## VIII. **Claim Construction**

[87] The Asserted Claims must be construed before their validity is assessed: *Whirlpool* at paras 43, 49. Patent claims must be read in an informed and purposive way, through the eyes of a person of skill in the art to which the patent relates: *Free World* at para 44; *Tearlab Corporation v I-MED Pharma Inc*, 2019 FCA 179 at paras 30-34 [*Tearlab*]. The relevant date for construing patent claims in this case is January 24, 2008, which is the date the patent application was published: *Whirlpool* at para 55; *Free World* at paras 53-54.

[88] Where infringement is in dispute, a purposive construction will determine whether claim elements are essential or non-essential: *Free World* at para 50; *Tearlab* at para 31. There is no infringement if an allegedly infringing product omits or substitutes an essential claim element: *Free World* at para 31. In view of the defendants' concession on infringement, the plaintiffs are not required to establish that the Accord Products or the Methofill Products fall within the scope of the Asserted Claims.

[89] In addition to expert evidence on the construction of the Asserted Claims, the parties introduced a joint claim chart with proposed constructions of key claim terms. However, the Court is not required to accept the experts' or the parties' proposed constructions. Claim construction is a question of law for the Court to decide: *Whirlpool* at para 61; *Zero Spill Systems (Int'l) Inc v Heide*, 2015 FCA 115 at para 41.

[90] The plaintiffs contend the Court should rely on Dr. Massarotti's and Dr. Sinko's claim construction opinions and use those constructions when analyzing the validity arguments. The plaintiffs criticize the construction approach taken by the defendants' experts, stating that while Drs. Roth and Rue explained how certain claim terms would be understood, they did not identify the essential elements of the claims. The plaintiffs contend their own experts construed the Asserted Claims in accordance with the proper legal principles.

[91] Despite this criticism, the plaintiffs state that the sole material disagreement on claim construction relates to the term 'about 50 mg/ml'. The plaintiffs do not advance a material disagreement on other aspects of Dr. Roth's and Dr. Rue's construction of the claims.

[92] The defendants also state that the only claim term in dispute is ‘about 50 mg/ml’ in claims 3 and 20. The defendants assert that claims 3, 20, and their corresponding dependent claims are invalid for ambiguity because ‘about 50 mg/ml’ is incapable of precise definition.

[93] Rather than addressing the parties’ arguments on ‘about 50 mg/ml’ in this section, I will address them in the section dealing with the ambiguity ground of invalidity.

[94] Drs. Sinko, Roth, and Rue provided similar opinions on claim construction, consistent with the plain language of the claims and the ordinary meaning of the claim terms. I do not discern a material difference between the parties’ joint claim chart and these experts’ opinions on how the skilled person would understand the Asserted Claims.

[95] Dr. Massarotti’s opinion on claim construction differed. In my view, Dr. Massarotti’s opinion on the construction of the Asserted Claims was sometimes inconsistent with a purposive construction.

[96] For example, Drs. Sinko, Rue, and Roth opined that ‘for the treatment of inflammatory autoimmune diseases’ in claim 1 describes what the medicament of claim 1 is intended to treat, what it is for, or what it can be used for. Dr. Massarotti construed the same language as an essential element of claim 1 that would be understood to mean using methotrexate to treat IADs, which suggests that administration to a patient is a claim element. Dr. Massarotti’s construction of claim 1 also differs from other experts’ constructions in that she defines ‘treatment’ to require both alleviating disease symptoms and controlling disease progression, and she limits the

meaning of ‘inflammatory autoimmune diseases’ to disease conditions that are specifically referred to in the 662 Patent disclosure.

[97] As another example, Dr. Massarotti construes ‘the medicament is present in a form suitable for patient self-administration’ in claim 7 to mean the medicament is present in an injection device, such as a syringe, that is designed to be conceptually easy to administer and to require minimal manual dexterity. Dr. Massarotti states this is important for patients with compromised functional ability. However, claim 7 does not include these limitations and it is clear from other claims (for example, dependent claims 13 and 14 state that the medicament may be in a storage container, such as a vial, containing up to 5,000 mg of methotrexate) that claim 7 is not limited to an injection device designed for easy administration by those with compromised dexterity. Claim 7 is broader than Dr. Massarotti proposes.

[98] Having considered the experts’ opinions on construction in light of the parties’ joint claim chart, I find the skilled person would construe the Asserted Claims as set out below. Claim elements are presumed to be essential: *Mediatube Corp v Bell Canada*, 2017 FC 6 at para 33. No experts opined that any elements of the Asserted Claims are not essential.

**Independent Claims 1 and 18**

***Claim 1***: Use of *methotrexate* for the *production* of a *subcutaneously administered* medicament for the *treatment of inflammatory autoimmune diseases*, wherein the methotrexate is present in a *pharmaceutically acceptable solvent* at a *concentration* of more than 30 mg/ml.

- *methotrexate* is the active pharmaceutical ingredient used in the medicament

- *production* refers to the process of making, developing, or manufacturing the end product (for example, a vial or pre-filled syringe) for use by a physician or patient

- *subcutaneously administered* (or subcutaneous administration) means a method of parenteral administration where the medication is injected under the skin, but not into muscle or a blood vessel

- *treatment of inflammatory autoimmune diseases* refers to the diseases intended to be treated

    - *inflammatory autoimmune diseases* are characterized by inflammation resulting from the body's immune system attacking its own cells; as used in the claim, this term includes, but is not limited to, the diseases referred to at page 5 of the 662 Patent: rheumatoid arthritis, juvenile arthritides, vasculitides, collagenoses, Crohn's disease, colitis ulcerosa, bronchial asthma, Alzheimer's disease, multiple sclerosis, Bechterew's disease, joint arthroses or psoriasis, as well as psoriasis arthritis and in particular plaque-type psoriasis vulgaris

- *pharmaceutically acceptable solvent* is a substance, usually a liquid, that dissolves a solute (in this case, methotrexate) and can be used with the active pharmaceutical ingredient and other components of a pharmaceutical formulation in patients generally without toxic reactions

- *concentration* is the amount of active pharmaceutical ingredient present per unit volume of solvent; in the claims, concentration is expressed as milligrams of methotrexate per millilitre of solvent (mg/ml)

***Claim 18***: *Ready-made syringe*, comprising a *pharmaceutical solution formulation* of methotrexate with a *concentration* of more than 30 mg/ml in a *pharmaceutically acceptable solvent* for *subcutaneous administration*.

- *ready-made syringe*, also referred to as a pre-filled syringe, is type of injection device; the syringe already contains a given dosage of the drug, ready for injection

- *pharmaceutical solution formulation* is, in the claim, a liquid solution formulation of methotrexate

- *subcutaneous administration, pharmaceutically acceptable solvent* and *concentration* have the same meaning as in claim 1, above

**Dependent Claims**

***Claims 2 and 19*** limit the methotrexate concentration of claims 1 and 18, respectively, to more than 30 mg/ml to 100 mg/ml.

***Claims 3 and 20*** further limit the methotrexate concentration to 'about 50 mg/ml'. The parties disagree on the construction of this term. Their arguments are addressed in the ambiguity section.

***Claims 4 and 22*** limit the pharmaceutically acceptable solvent of claims 1-3 or 18-20, respectively, to water, water for injection purposes, or water comprising isotonization additives and sodium chloride solution.

- *water for injection* is water that is prepared in such a way as to make it essentially free of pyrogenic endotoxins

- *isotonization additives* are additives to adjust the tonicity of the formulation, that is, the relative osmotic pressure between multiple solutions, to minimize injection pain

- *sodium chloride solution* is a water-based solution in which sodium chloride is added

***Claim 5*** limits the inflammatory autoimmune diseases of claims 1-4 to rheumatoid arthritis, juvenile arthritides, vasculitides, collagenoses, Crohn's disease, colitis ulcerosa, bronchial asthma, Alzheimer's disease, multiple sclerosis, Bechterew's disease, joint arthroses, or psoriasis.

***Claim 6*** further limits the inflammatory autoimmune disease of claim 5 to rheumatoid arthritis.

***Claim 7*** depends on claims 1-6, and adds a limitation that the medicament is present in a form suitable for patient self-administration.

- *a form suitable for patient self-administration* is a form the patient is capable of administering on their own, including outside the clinic and without supervision from the physician or nurse

***Claim 8*** depends on claims 1-7 and further specifies that the medicament is contained in an injection device for a single application.

- *injection device* is a device used to inject the drug (methotrexate) into a patient, such as a syringe

- *single application* means the injection device is disposed of after a single injection

***Claims 9 and 21*** add that the injection device of claim 8 or the ready-made syringe of claims 18-20 contain a methotrexate dosage of 5 to 40 mg.

- *dosage* is amount by weight of the active drug ingredient administered to a patient; in this case, doses of methotrexate are typically expressed in milligrams (mg)

***Claim 10*** limits the injection device of claims 8 or 9 to a ready-made syringe.

***Claims 35 and 39*** specify that the methotrexate dosage of claims 9 or 21, respectively, is 5.0, 7.5, 10.0, 12.5, 15.0, 17.5, 20.0, 22.5, 25.0, 27.5, 30.0, 32.5, 35.0, 37.5 or 40.0 mg of methotrexate.

## IX. **Validity**

### A. *Skilled Person*

#### (1) The parties' submissions

[99] The parties and their experts agree that the skilled person comprises a team. They further agree that one team member would be a clinician who has experience with methotrexate in the treatment of IADs, likely a rheumatologist.

[100] There is disagreement on the second member of the skilled person team.

[101] The plaintiffs submit the second member is someone with a background in pharmacy and/or pharmaceutical sciences who has experience with and can prepare methotrexate formulations.

[102] The defendants submit the 662 Patent is a formulation patent that is directed to a pharmaceutical formulator, not a pharmacist. According to the defendants, the distinction between a pharmacist and a pharmaceutical formulator is important because a pharmacist is limited to commercially available products, but a formulator who regularly works with active pharmaceutical ingredients (API) is not.

[103] The defendants further submit that the plaintiffs' evidence on the skilled person should be afforded little or no weight because their position on the attributes of the skilled person is an abuse of process. In a patent action before the England and Wales High Court of Justice (EWHC), where the validity of a foreign counterpart to the 662 Patent having the same owner, inventor, priority date, and disclosure was at issue, the EWHC disagreed with medac's position that the skilled person is a clinician alone: *Accord Healthcare Ltd v medac Gesellschaft Für Klinische Spezialpräparate Mbh*, [2016] EWHC 24 (Pat) at paras 14-15, 20-21. The EWHC found the counterpart to the 662 Patent to be a formulation patent addressed to a team comprising a clinician and a formulator working at a pharmaceutical manufacturer: *Ibid*. The defendants say a skilled person's attributes are determined by the subject matter of a patent and the plaintiffs' position in this action constitutes an abuse of process because it is contrary to a previously-decided issue: *AstraZeneca Canada Inc v Apotex Inc*, 2015 FC 322 at paras 377-380 [*AstraZeneca*].

[104] The plaintiffs state *AstraZeneca* is distinguishable. They contend this Court is not bound by the decision of a foreign court in related patent litigation, and in any event, there have been mixed results in litigation over foreign counterparts to the 662 Patent.

(2) Analysis

[105] Beginning with the abuse of process argument, I agree with the plaintiffs that *AstraZeneca* is distinguishable. In *AstraZeneca*, the estoppel argument related to a foreign court's prior findings of fact about the characteristics of an allegedly infringing product—and even so, the Court in *AstraZeneca* declined to apply foreign issue estoppel. The Court was not considering whether a party was estopped from raising arguments about the skilled person's attributes, which involve considerations of foreign law. Even if a Canadian patent and a foreign counterpart are practically identical, foreign law is unlikely to be so and must be proved: *Eli Lilly Canada Inc v Mylan Pharmaceuticals ULC*, 2015 FC 17 at para 66. The defendants have not proven foreign law for the EWHC proceeding and they have not established that the plaintiffs' position on the skilled person constitutes an abuse of process.

[106] Turning to the composition of the skilled person team, I agree with the parties and the experts that the notional skilled person for the 662 Patent represents a team with one member being a clinician who has experience treating IAD patients with methotrexate.

[107] As Dr. Roth points out, the 662 Patent discusses treatment by administering methotrexate at various doses, concentrations, and routes of administration, and an active prescriber of methotrexate would understand these concepts. Dr. Roth states, and I agree, that the 662 Patent is not addressed to a general medical practitioner who does not have some specialized experience

with methotrexate to understand its use and administration for the treatment of IADs. While the 662 Patent includes several claims that are not limited to methotrexate for the treatment of IADs and not limited to methotrexate doses that would be used to treat IADs, in my view the 662 Patent as a whole is more focussed on injectable methotrexate solutions for the treatment of IADs.

[108] Dr. Massarotti and Dr. Roth both opined that the clinician team member is likely a rheumatologist. They opined that rheumatoid arthritis, one of the most common IADs, is commonly treated with methotrexate, often as a first line of therapy. Their evidence was that a rheumatologist would have knowledge about methotrexate for the treatment of IADs and experience as a regular prescriber of methotrexate, including by injection. I accept this evidence. As of 2006, methotrexate was considered to be the "gold standard" for treating rheumatoid arthritis. A rheumatologist of ordinary skill would have the appropriate level of skill and the appropriate level of experience with methotrexate and its use in treating IADs that is embodied by the skilled person.

[109] Turning to the second member of the skilled team, the plaintiffs' experts opined that the skilled team likely consists of a rheumatologist and a pharmacist. Dr. Sinko described the second team member as someone with "1-2 years experience preparing and filling prescriptions for methotrexate (including methotrexate for injection) for the various diseases it is used to treat, likely a pharmacist". In Dr. Massarotti's view, the second team member also could be a pharmacy technician or a nurse, provided that, in addition to their academic qualifications, they have several years of experience in methotrexate preparation. Dr. Sinko stated it is generally the role of the clinician, in this case the rheumatologist, to determine which medication to use to

treat a patient, and the pharmacist would then prepare the medication according to the prescription and dispense it to the patient.

[110] Both Dr. Sinko and Dr. Massarotti opined that by 2006, methotrexate was an old drug and commercially available in formats including tablets or solutions for injection at a concentration of 25 mg/ml. They opined that a skilled pharmacist is someone who would use the readily available commercial products to fill a prescription and would not prepare new formulations unless asked to do so by the clinician. In Dr. Massarotti's view, a pharmacist in 2006 would rarely need to prepare a formulation for IADs from methotrexate powder. Dr. Sinko stated that a pharmacist would be more involved in researching and suggesting new approaches to the clinician in circumstances where there was no commercially available product for a particular drug or route of administration, or only limited clinical experience to support its use.

[111] The plaintiffs' experts have not presented a compelling reason why the second skilled team member would be a pharmacist (or pharmacy technician or nurse) with 1-2 years of experience filling methotrexate prescriptions and whose experience with pharmaceutical formulations would largely be reconstituting readily available commercial products (which, according to Dr. Massarotti, would be done only rarely). I find the 662 Patent is not addressed to such a person.

[112] I prefer the evidence of Drs. Rue and Roth explaining why the skilled person team would comprise a pharmaceutical formulator. A skilled formulator is a person who would have learned how to formulate drugs and would have practical laboratory experience doing so. The formulator's knowledge would include an understanding of different routes of administering

drugs, common formulations used to achieve clinical needs (such as a desired dose, frequency, and treatment regimen), the pharmacology of drugs, and side effects of drugs and their formulations. A pharmaceutical formulator would also have a basic understanding of pharmacokinetics (drug absorption, distribution, metabolism, and excretion). Dr. Roth opined, and I agree, that a pharmacist would not have the experience necessary to prepare large-scale quantities of methotrexate products according to the example formulations described in the 662 Patent.

[113] While I recognize that the 662 Patent does not solve a problem of formulating methotrexate solutions at the concentrations claimed in the 662 Patent—indeed, by 2006 methotrexate was commercially available as a medicine at concentrations described and claimed in the 662 Patent—the 662 Patent disclosure states that the object of the invention is to provide a pharmaceutical formulation for the treatment of IADs that overcomes the disadvantages of prior art preparations. It describes pharmaceutically acceptable solvents, additives that are common in the pharmaceutical formulation field, and provides examples for preparing 30 litre batches of 50 mg/ml methotrexate solution using kilogram quantities of methotrexate powder, which would be enough product for tens of thousands of doses in the dose range typically prescribed for IADs. In my view, a pharmaceutical formulator possesses the ordinary level of skill and knowledge in the art or science to which the 662 Patent relates and I find the patent is addressed to a skilled team that includes such a person.

[114] The plaintiffs contend there is no basis in the evidence to limit the second team member to a pharmaceutical formulator and thereby exclude the kind of pharmacist who commonly and

regularly prepared methotrexate formulations during the material time—including pharmacists working in hospitals or in compounding pharmacies.

[115] I accept that there is overlap in the knowledge and skillset of workers in various pharmaceutical sciences. Even though Dr. Sinko described the second team member as a pharmacist, he agreed that the skilled person would have skill and experience in formulations and would be able to make liquid solutions of different concentrations of methotrexate that are suitable for subcutaneous administration. On cross-examination he stated that: regardless of whether the skilled team member is a pharmacist or formulator, they would need to understand solubility and they would need skills working with API, making liquid solutions, and making solutions for parenteral administration; a pharmacist working in a typical community pharmacy would not work with API, but a pharmacist in a specialty compounding pharmacy such as an oncology compounding pharmacy could get raw API; and the equipment needed to work with kilogram quantities of API would typically be found in an industrial or academic research setting. Similarly, Dr. Massarotti stated in cross-examination that the 662 Patent is directed to someone who has the knowledge and experience required to prepare methotrexate solutions at various concentrations above 30 mg/ml, including large-scale commercial batches, and a pharmacist working in a pharmacy would not be preparing large-scale commercial batches of methotrexate solution.

[116] A pharmacist who dispenses methotrexate prescriptions would not ordinarily have experience preparing methotrexate from API. To the extent that a specialized pharmacist at a hospital or compounding pharmacy who prepares methotrexate formulations from API would have skill and knowledge that aligns with the 662 Patent, in my view the skill and knowledge of

such a pharmacist would be subsumed in the skilled person team comprising a rheumatologist and a pharmaceutical formulator.

[117] For these reasons, I find the person of ordinary skill in the art or science to which the 662 Patent relates is represented by a team comprising a rheumatologist and a pharmaceutical formulator, each having, in addition to their education credentials, about 1-2 years of experience in their respective fields.

B. *Common General Knowledge*

(1) The parties' submissions

[118] The plaintiffs submit that the evidence of Drs. Massarotti and Sinko on the skilled person's CGK should be preferred. They contend the evidence of Drs. Massarotti, Sinko, and Roth was largely consistent and should be preferred over Dr. Rue's evidence because Dr. Rue has no experience with methotrexate and he deferred to the clinician on the treatment of diseases.

[119] The defendants contend there is little in dispute regarding the CGK. In fact, they say most of the relevant CGK is admitted in the 662 Patent.

(2) Analysis

[120] As explained later in this section, Drs. Roth, Massarotti, and Sinko were not aligned on certain aspects of the CGK and on these points I generally prefer Dr. Roth's evidence. I disagree with the plaintiffs that Dr. Rue's evidence should be discounted because he did not have experience formulating methotrexate specifically. The evidence did not establish any issue with formulating methotrexate solutions, and as noted above, the 662 Patent did not solve a

methotrexate formulation problem. Dr. Rue gave evidence from the skilled formulator's perspective and the plaintiffs did not object to his pharmaceutical formulation expertise. His evidence was relevant, helpful, and supported by the pre-July 2006 literature.

[121] The 662 Patent disclosure sets out key information that formed part of the relevant state of the art; however, I do not agree with the defendants that the patentee admitted that all such information was also part of the skilled person's CGK.

[122] Nonetheless, there is considerable overlap in the parties' positions and the experts' opinions on the information that did form part of the skilled person's CGK. The experts qualified to opine on the skilled clinician's or the skilled formulator's CGK agreed that the following would have been CGK as of the July 2006 priority date, and would not have changed as of the January 2008 publication date:

i. As noted in the background section above, methotrexate is an old drug. Methotrexate was and still is a well-known drug for cancer and IADs.

ii. Classified as a DMARD, by the 1980s methotrexate had become a standard treatment for rheumatoid arthritis, psoriasis, and other IADs.

iii. The doses of methotrexate used to treat IADs are typically much lower than the doses used to treat cancer. The treatment goals are different—very high doses of methotrexate are used to kill cancer cells, whereas much lower doses of methotrexate are used to target the inflammatory processes in IADs.

iv. Methotrexate was considered a "cornerstone" or "gold standard" treatment for rheumatoid arthritis. It was often prescribed as an early or first line treatment for rheumatoid arthritis, as well as for other IADs. As Dr. Massarotti put it,

"Methotrexate is one of the most important drugs in the treatment of rheumatoid arthritis and many other inflammatory autoimmune diseases. The question for many rheumatologists by 2006-2008 was not whether to use methotrexate, but whether there are any reasons not to use it."

v. Methotrexate can be administered orally or parenterally. Parenteral administration refers to routes of administration that avoid the gastrointestinal tract.

vi. Parenteral administration of methotrexate improves bioavailability and results in fewer gastrointestinal side effects when compared to oral administration, particularly at doses greater than 15-20 mg.

vii. Common parenteral routes of administration for methotrexate are by intravenous, intramuscular, or subcutaneous injection.

viii. When prescribed for rheumatoid arthritis and other IADs, methotrexate is administered orally, or by intramuscular or subcutaneous injection. The most common parenteral route is subcutaneous injection, which is preferred over intramuscular injection because it is less painful and can be self-administered.

ix. Patients taking methotrexate for an IAD typically remain on the drug indefinitely. A conventional methotrexate prescription for IADs would be a weekly dose, administered as oral tablets or a subcutaneous injection of a solution containing the prescribed dose. Patients may prefer to start with oral methotrexate, but if there is any question of efficacy or tolerability, subcutaneous methotrexate would be substituted.

x. Methotrexate was commonly available as 2.5 mg tablets for oral administration and vials containing a 25 mg/ml solution for subcutaneous or intramuscular injection. Vials of methotrexate solution could be used by healthcare providers administering the drug to patients, by pharmacists pre-filling syringes with a prescribed dose to be administered to patients, or by patients (or their family members or other caregivers) drawing up a prescribed dose to administer. Dr. Massarotti noted a conventional practice of using a 1 ml capacity syringe with volume markings at 0.1 ml increments to draw up the prescribed dose of methotrexate from a vial containing 25 mg/ml methotrexate solution, and stated this was practical because the doses most commonly prescribed for IADs could be administered with a single injection. Commercially prepared syringes pre-filled with methotrexate solution were available but more costly.

xi. The subcutaneous route of administration is not suitable for administering large volumes; typically, subcutaneous administration involves small volumes of 1 ml or less.

xii. Injections may be associated with injection pain. The volume of solution injected into muscle or under the skin was known to be a factor, but not the only factor, that could influence injection pain.

xiii. Making liquid solutions of methotrexate at different concentrations, including for subcutaneous administration, would be routine.

[123] I accept that the above formed part of the skilled person's CGK as of 2006 and also as of 2008.

[124] There was disagreement, or at least a discrepancy, between the parties and their experts about whether or to what extent the following formed part of the skilled person's CGK: (a) the extent of the skilled person's knowledge about commercially available methotrexate products; (b) certain details about what constituted conventional prescribing practices for IADs; (c) how the skilled person would regard information about methotrexate for cancer treatment or methotrexate products for cancer treatment—including whether, due to toxicity concerns, the skilled person would have avoided using methotrexate doses and concentrations intended for treating cancer to treat IADs; (d) whether methotrexate formulations for intramuscular and subcutaneous injection were considered to be interchangeable.

(a) *Knowledge of commercially available methotrexate products*

[125] The defendants contend the skilled person would have known the range of commercially available methotrexate solutions for treating IADs, which came in vials and ready-made syringes at various concentrations of methotrexate solution and various doses of methotrexate. Dr. Sinko's opinion is consistent with the defendants' position—his report states the CGK includes the properties of methotrexate and its uses to treat various diseases, including IADs, as well as the routes of administration and products available for treating these diseases. In Dr. Massarotti's opinion, however, the skilled person would be familiar with products that were commercially available where they worked, but they may not be familiar with products in different markets and they would have no reason to look up product labels or information about various methotrexate products as part of their standard practice.

[126] In my view, nothing turns on this point. While the skilled person may not have known every methotrexate product commercially available as of 2006 as part of their CGK, they would

have readily found information about commercially available methotrexate tablets and a range of commercially available methotrexate liquid solutions, at various doses and concentrations, by exercising reasonable diligence. For commercially available pre-filled syringes specifically, the 662 Patent states, and Dr. Massarotti agreed, that as of the priority date pre-filled syringes containing methotrexate solutions at concentrations of 7.5 mg/ml, 10 mg/ml and 25 mg/ml were commercially available in Germany. Both Drs. Massarotti and Sinko state the skilled person would not be aware of commercial, pre-filled syringes containing a solution more concentrated than 25 mg/ml. However, with reasonable diligence, the skilled person would have found commercially available vials of methotrexate solution at concentrations of 50 mg/ml and 100 mg/ml (for example, Wyeth and Hospira).

(b) *Details about conventional methotrexate prescribing practices for IADs*

[127] The 662 Patent states that a dosage range of 5 to 30 mg/week was common for antirheumatic therapy in Germany, and in other European countries dosages of up to 40 mg of methotrexate were administered. In Dr. Roth's opinion, the skilled person would know that the common methotrexate dosage for treating IADs was from 7.5 to 25 mg/week and would also know that doses up to 40 mg/week could be used in more severe cases; however, higher doses were associated with increased side effects and many clinicians would only rarely prescribe a dose exceeding 25 mg/week. In her written report, Dr. Massarotti disagreed with Dr. Roth that doses up to 40 mg/week could be used in more severe cases. In her view, it was known by 2006 that a dose above 25 mg/week was unlikely to provide any additional benefit and higher doses were associated with increased side effects and toxicity. For patients who did not respond to 25 mg/week of methotrexate, Dr. Massarotti stated the skilled person would have used an alternative strategy such as adding or substituting another DMARD or a biologic drug. Dr.

Sinko's opinion was that it would have been rare to treat IADs with methotrexate doses exceeding 25 mg.

[128] The differences between the opinions expressed in the experts' reports effectively disappeared after cross-examinations. Drs. Massarotti and Sinko were taken to pre-July 2006 publications reporting higher doses being used to treat IADs and both acknowledged that methotrexate doses could go above 25 mg/week. Dr. Roth reiterated his view that clinicians could prescribe a higher dose but would have done so rarely.

[129] I find that as of 2006, the skilled person would have considered that the conventional practice for treating rheumatoid arthritis was to prescribe up to 25 mg/week of methotrexate and rarely higher. The conventionally prescribed dose for other IADs, including psoriasis, could exceed 25 mg/week. The skilled person would have known that side effects and/or toxicity might be seen even at the lower end of the conventional dose range, and higher doses of methotrexate were known to be associated with an increased risk of side effects and/or toxicity.

(c) *Information about methotrexate for cancer treatment and methotrexate products for cancer treatment*

[130] As noted above, the parties and the experts agree that the skilled person would have known that methotrexate was used to treat cancers, generally at much higher doses than those used to treat IADs. However, the parties disagree on how the two treatment indications affected the skilled person's mindset. The plaintiffs contend methotrexate was used in very different ways to treat cancer and IADs, while the defendants contend there was overlap. The parties'

differences on this point also led to differences in how each side defined the relevant state of the art for the obviousness analysis.

[131] Each side's experts' opinions align with the parties' positions.

[132] Dr. Massarotti's view was that the skilled person was "acutely aware" of the distinction between how methotrexate is used for treating cancer versus IADs, and would not conflate the two. Dr. Sinko expressed a similar opinion, stating the skilled person would know not to use methotrexate for IADs in the way it is used for cancer. Both experts opined that, due to toxicity concerns, the skilled person would not have used methotrexate at doses and concentrations intended for treating cancer to treat IADs.

[133] Dr. Roth's view was that methotrexate is generally prescribed at far higher doses for cancer, but he did not agree there was a clear divide. He noted that methotrexate product labels often described a range of treatment indications for the same product—including cancer, rheumatoid arthritis, psoriasis, and other IADs.

[134] In their opinions on validity, Dr. Roth and Dr. Rue considered the available methotrexate products and publications, even if they were not expressly for IADs or if they provided information on methotrexate for cancer treatment. Drs. Massarotti and Sinko excluded some of these references on the basis that the skilled person would not consider oncology products and uses to be part of the state of the art for IADs. Dr. Sinko stated the skilled person would not have looked to publications in the field of cancer treatment, which differed in significant ways from the treatment of IADs.

[135] With respect to dose, as previously noted, all experts agreed that the doses of methotrexate used to treat cancer were generally much higher than the doses used to treat IADs. However, the low end of the dose range for cancers and the high end of the dose range for IADs overlap. On cross-examination, Dr. Massarotti and Dr. Sinko acknowledged that for some cancers, methotrexate is administered at the same doses that are used for IADs, but more frequently. Drs. Massarotti and Sinko did not cite any literature references to support their opinions that the skilled person would avoid methotrexate at concentrations used for cancer treatment.

[136] I find the plaintiffs and their experts overstate the distinction between methotrexate's use in treating cancer and its use in treating IADs. In my view, the pre-2006 literature on methotrexate is more consistent with the defendants' position. Many pre-2006 publications discuss methotrexate's use for both indications. While the publications note differences in how methotrexate is used to treat cancer and IADs, they also provide significant information about methotrexate's properties that is relevant to both. Dr. Sinko conceded on cross-examination that it was not unusual for the same article to look at both indications. Product labels and pharmaceutical reference texts describing available methotrexate products discuss both indications, consistent with Dr. Roth's opinion. In my view, it is significant that the same methotrexate product was sometimes used for both cancer and IAD indications—including some methotrexate products medac had on the market. Mr. Will testified that medac's 2.5 mg and 10 mg methotrexate tablets developed for leukemia were later used mainly for treating IADs. He also stated that in the early 2000s rheumatologists may have used vials containing 2.5 mg/ml and 25 mg/ml methotrexate solutions from medac's oncology line for treating IAD patients.

[137] The literature indicates that methotrexate's side effects and toxicity may be affected by dose, frequency of administration (the body has less time to rebound if methotrexate is given daily rather than weekly), or prolonged use, but it does not support that methotrexate's side effects and toxicity were considered to be concentration-dependent or that methotrexate formulations more concentrated than 25 mg/ml were considered to be cancer formulations. In my view, the fact that methotrexate's toxicity and certain of its side effects were known to be dose-dependent would not have caused the skilled person to exclude oncology references from the relevant state of the art. The skilled person's CGK would not have steered them away from oncology literature or products, and the skilled person would not have considered such literature or products to be outside the relevant state of the art.

(d) *Whether methotrexate formulations for intramuscular and subcutaneous injection were considered interchangeable*

[138] The defendants state it was CGK that parenteral methotrexate formulations are effectively interchangeable. Dr. Roth opined that, in 2006, product labels for methotrexate products generally included multiple approved indications and routes of administration. The same liquid formulation of methotrexate could be used intravenously, intramuscularly, and subcutaneously, and these methods of administration could be interchanged in clinical practice. According to Dr. Roth, the subcutaneous route was preferred and methotrexate products were administered this way using products that were not specifically indicated for subcutaneous use.

[139] Dr. Sinko's report states that parenteral routes of administration are generally not interchangeable and the skilled person would not administer a drug intended for one route by another route without some evidence that doing so would be safe and effective. He wrote that a

drug administered subcutaneously is generally absorbed more slowly and remains concentrated at the site for longer, which can increase the risk of toxicity or injection site issues. Dr. Sinko expressed this opinion more definitively in his in-chief testimony, stating that parenteral routes are not interchangeable.

[140] I prefer Dr. Roth's evidence that methotrexate administration via the intramuscular and subcutaneous routes were considered interchangeable. His opinion is supported by pre-2006 literature references, including widely cited studies that compared the pharmacokinetics of different routes of methotrexate administration in patients. For example, Brooks 1990 compared pharmacokinetic parameters for intramuscular and subcutaneous administration of methotrexate in patients with rheumatoid arthritis. The authors of that study reported that methotrexate concentrations achieved by intramuscular and subcutaneous delivery were statistically and clinically similar, and concluded that intramuscular and subcutaneous injections are interchangeable routes of methotrexate administration.

[141] On cross-examination, Dr. Sinko was directed to both Brooks 1990 and Balis 1988. The latter studied the pharmacokinetics of subcutaneously administered methotrexate as an alternative to oral methotrexate in animals and in human patients with leukemia. Dr. Sinko found reason to discount the authors' conclusions about interchangeability. I do not accept his evidence on this point. In my view, Dr. Sinko's concerns about interchanging routes of administration are inconsistent with the pre-2006 literature on methotrexate and the evidence about how methotrexate was used in practice. The evidence indicates that it was an accepted clinical practice, as of 2006, to administer the same methotrexate formulation intramuscularly or subcutaneously. Dr. Massarotti stated that she would almost always use a product for

subcutaneous administration if the product was indicated for either of these routes of administration.

[142] I find the skilled person would have considered methotrexate liquid formulations for intramuscular and subcutaneous injection to be commonly interchangeable. Whether in vials or ready-made syringes, these methotrexate preparations could be administered subcutaneously. The subcutaneous route of administration was well known and the skilled person would have prescribed methotrexate formulations via subcutaneous administration even if they were not specifically indicated for that route of administration.

C. *Obviousness*

(1) Legal Principles

[143] The subject matter that is defined by a patent claim must be subject matter that would not have been obvious on the claim date to a person skilled in the art or science to which it pertains, having regard to the relevant prior art: *Patent Act*, RSC 1985, c P-4, s 28.3 [*Patent Act*].

[144] As the Federal Court of Appeal stated in *Beloit* (at page 294), the test for obviousness is not to ask what competent inventors did or would have done. Inventors are by definition inventive. The question to be asked is whether the skilled person, having no inventiveness, in light of the state of the art and the CGK at the material date, would have come directly and without difficulty to the solution taught by the patent.

[145] *Sanofi* (at paragraph 67) sets out a four-step framework for determining whether the subject matter of a claim is obvious:

> (1) (a) Identify the notional "person skilled in the art";
> (b) Identify the relevant common general knowledge of that person;
> (2) Identify the inventive concept of the claim in question or if that cannot readily be done, construe it;
> (3) Identify what, if any, differences exist between the matter cited as forming part of the "state of the art" and the inventive concept of the claim or the claim as construed;
> (4) Determine whether, when viewed without any knowledge of the alleged invention as claimed, those differences would have been obvious to the person skilled in the art, or whether they require any degree of invention.

[146] Under step 4, it may be appropriate to consider, as one factor to assist the obviousness inquiry in fields where advances often occur through experimentation, whether the alleged invention would have been "obvious to try": *Sanofi* at paras 68-69; see also *Apotex Inc v Pfizer Canada Inc*, 2019 FCA 16 at para 32 [*Apotex v Pfizer*]. Relevant considerations for an "obvious to try" inquiry can include (*Sanofi* at para 69):

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

[147] Other factors that may be considered include the actual course of conduct that culminated in the making of the invention and other secondary considerations: *Sanofi* at para 70; *Apotex v Pfizer* at para 32.

[148] The *Sanofi* framework contemplates a flexible approach that must be applied contextually to the facts and circumstances of each claim: *Amgen Inc v Pfizer Canada ULC*, 2020 FCA 188 at para 5; *Apotex v Pfizer* at para 39. It is applied to the combination of the elements defining the invention, rather than to each of its discrete elements: *Allergan Inc v Sandoz Canada Inc*, 2020 FC 1189 at para 154, citing *Teva Canada Limited v Janssen Inc*, 2018 FC 754 at para 86.

(2) The parties' submissions

[149] The defendants assert that the subject matter of the Asserted Claims is not inventive. They submit the 662 Patent claims a known drug (methotrexate) in known solvents (water and sodium chloride) for known treatment indications (IADs) using a known route of administration (subcutaneous) packaged in a known format (single use syringes for self-administration) at known dosages (5-40 mg) and a known concentration (50 mg/ml) to provide a known benefit (reducing injection pain). medac discovered no new therapeutic effects and found no unexpected results. It commissioned three routine tests before the Canadian filing date because these were required for regulatory approval, not because there was any doubt the purported invention would work. The defendants contend the invention claimed in the 662 Patent was a line extension of existing medac products, developed to fill a market gap. They allege medac has taken a twenty-year monopoly over a purely commercial opportunity for which the public has received nothing in exchange.

[150] The defendants state there is nothing new or inventive in the combination of the above elements, which were known and used in combination before the claim date. The skilled person would not have to combine knowledge from different fields or combine knowledge from different prior art references in the same field. According to the defendants, the gap between a

number of single prior art references and the inventive concept could be bridged using only the skilled person's CGK—for example starting from Wyeth, Jansen 1999, Hoekstra 2004, or Russo 2000.

[151] The defendants contend the plaintiffs' experts created a distance between the state of the art and the alleged invention that is not there, and it affected their opinions on anticipation and obviousness. The plaintiffs' experts created distance by describing one skilled team member to be a pharmacist who dispenses available products. They also overstated the distinction between oncology and rheumatology products, and improperly excluded literature and products from the state of the art on the basis that the skilled person would not apply information about methotrexate's use in cancer to its use for the treatment of IADs. Therefore, their opinions on obviousness should be given no weight where they conflict with the opinions of Drs. Roth or Rue, or where the opinions are unsupported by the literature.

[152] The plaintiffs submit Mr. Will's invention is novel, inventive, and useful, and meets the definition of invention in section 2 of the *Patent Act*. They assert it was Mr. Will's unique background, training, and experience that allowed him to identify a problem in the field and find a solution to that problem when others did not. While some may view the invention as a simple or incremental advance, this does not negate an otherwise meritorious invention.

[153] The plaintiffs caution that hindsight must not creep into an obviousness analysis. They rely on the question posed in *Beloit* (at page 8) to refute obviousness:

> Every invention is obvious after it has been made, and to no one more so than an expert in the field. Where the expert has been hired for the purpose of testifying, his infallible hindsight is even

> more suspect. It is so easy, once the teaching of a patent is known, to say, "I could have done that"; before the assertion can be given any weight, one must have a satisfactory answer to the question, "Why didn't you?"

[154] The plaintiffs submit that Dr. Rue, who does not have experience preparing methotrexate solutions and was no longer working as a formulator at the material times, is the witness hired for the purpose of testifying as described in *Beloit*. He could only analyze the validity issues with the benefit of hindsight. The plaintiffs say their own experts' evidence should be preferred over that of Dr. Rue.

[155] The plaintiffs contend Dr. Roth's cross-examination revealed that his actual opinions were materially inconsistent with the opinions set out in his expert report, particularly regarding the prior art and the inventive concept, which was the foundation for his obviousness opinion. The plaintiffs argue that Dr. Roth was a relatively credible witness whose overall opinion was more consistent with the plaintiffs' position than the defendants' position.

[156] The plaintiffs rely on *Swist v MEG Energy Corp*, 2021 FC 10 at paragraphs 211-214 to argue that the absence of any motivation to find the solution taught by the 662 Patent, combined with the fact that no one but Mr. Will did it, renders the obvious analysis futile. They submit Dr. Roth answered the *Beloit* question during cross-examination—no one came up with Mr. Will's invention because the skilled person was not motivated to depart from the standard 25 mg/ml methotrexate formulation.

[157] The defendants counter that the plaintiffs' arguments on motivation and the *Beloit* question are not supported by the evidence, and in any event, they are factors that *may* be considered in assessing obviousness and cannot make something inventive on their own.

[158] Both sides approached the question of obviousness by considering the narrowest claims of the 662 Patent.

[159] The defendants state that each of the Asserted Claims would have been obvious because the narrowest claims would have been obvious. The defendants' arguments focussed on the narrowest iteration of claim limitations for each of the two groups of Asserted Claims. Incorporating every dependency, these claims would read:

> **Claims 1-10 and 35**: Use of methotrexate for the production of a subcutaneously administered medicament for the treatment of inflammatory autoimmune disease such as rheumatoid arthritis, in a pharmaceutically acceptable solvent such as water for injection or sodium chloride solution, at a concentration of about 50 mg/ml, in a form suitable for patient self-administration, contained in an injection device for single application, and where the injection device is a ready-made syringe that contains a dosage of 5.0, 7.5, 10.0, 12.5, 15.0, 17.5, 20.0, 22.5, 25.0, 27.5, 30.0, 32.5, 35.0, 37.5 or 40.0 mg, of methotrexate.
>
> **Claims 18-22 and 39**: Ready-made syringe with a pharmaceutical solution formulation of methotrexate with a concentration of about 50 mg/ml in a pharmaceutically acceptable solvent such as water for injection or sodium chloride solution that contains a dosage of 5.0, 7.5, 10.0, 12.5, 15.0, 17.5, 20.0, 22.5, 25.0, 27.5, 30.0, 32.5, 35.0, 37.5 or 40.0 mg, of methotrexate.

[160] The defendants' restatement of Claims 1-10 and 35 is narrower than the restatement of claims 18-22 and 39 because the latter claim group is not limited by treatment indication.

Claims 1-10 and 35 include a limitation that the medicament is for the treatment of IADs, or twelve named treatment indications, or rheumatoid arthritis.

[161] The plaintiffs contend that in order to successfully defend this action, the narrowest claim the defendants must invalidate is claim 10 as it depends on claims 8, 7, 6, 5, 4, 3, 2, and 1 (some of which have multiple dependencies). They restate claim 10, incorporating all the claim limitations of claims 1-8, as follows:

> Use of methotrexate for the production of a subcutaneously administered medicament that is contained in a ready-made syringe for a single application and that is in a form suitable for patient self-administration, for the treatment of rheumatoid arthritis, wherein the methotrexate is present in a pharmaceutically acceptable solvent selected from water, water for injection purposes, water comprising isotonization additives and sodium chloride, at a concentration of about 50 mg/ml.

[162] The only substantive difference between the parties' restatements of the narrowest Asserted Claim in the group that includes a treatment indication limitation is that the plaintiffs' restatement of claim 10 omits the dosage limitations of claims 9 or 35. Each party's restatement otherwise incorporates all of the claim limitations of claims 1-10, although presented in a different order.

[163] The dosage range limitation of claim 9 is 5 to 40 mg of methotrexate. I note that the defendants' restatement incorporates the limitation of claim 35, which is narrower because it specifies 2.5 mg incremental dosages within the 5 to 40 mg range; however, no party asserts and the evidence does not suggest that the further limitation of claim 35 would "save" the Asserted Claims if they are otherwise found to be invalid for obviousness. Consequently, for the purposes of the validity analyses, there is no material difference between the defendants' restatement of

claims 1-10 and 35 and the plaintiffs' restatement of claims 10 and 1-8 if modified to add the dosage limitation of claim 9:

> Use of methotrexate for the production of a subcutaneously administered medicament that is contained in a ready-made syringe for a single application and that is in a form suitable for patient self-administration, for the treatment of rheumatoid arthritis, wherein the methotrexate is present at a dosage of 5 to 40 mg in a pharmaceutically acceptable solvent selected from water, water for injection purposes, water comprising isotonization additives and sodium chloride, at a concentration of about 50 mg/ml.

[164] The above description is the narrowest iteration of Asserted Claim 10, as it depends on claims 1-9, to consider for the obviousness analysis. Even though some iterations of claim 10 as it depends on claims 1-9 would be broader (for instance, the narrowest concentration limitation of 'about 50 mg/ml' is in claim 3), the parties referred to the narrow iteration as claim 10. I will refer to the narrow iteration as claim $10^{1\text{-}9}$.

(3) Step 1: The skilled person and their CGK

[165] The skilled person is a team comprising a rheumatologist and a pharmaceutical formulator. The CGK of the skilled person is set out above.

(4) Step 2: Inventive concept

[166] Before summarizing the parties' positions on inventive concept, I would note my agreement with the defendants that little turns on identifying the inventive concept and resolving the differences between the parties' positions on this point. Partly, this is because the parties' positions on inventive concept are closer than the plaintiffs suggest. More importantly, and as will be discussed under steps 3 and 4 of the obviousness analysis, most of the other elements of the Asserted Claims were already part of the state of the art in combination at a lower

concentration. In fact, most elements of the Asserted Claims, in combination, were part of the skilled person's CGK as a conventional way to treat patients with rheumatoid arthritis and other IADs.

[167] The defendants submit that identifying the inventive concept is a distinct exercise from claim construction. This step in the obviousness analysis is meant to "help determine what, if anything, makes the claim, as constructed, inventive", and it is not materially different from identifying the solution taught by the patent: *Apotex Inc v Shire LLC*, 2021 FCA 52 at paras 74-77 [*Apotex v Shire*].

[168] The defendants submit the 662 Patent identifies a prior art problem that large injection volumes can cause pain or discomfort, and it teaches a solution of increasing concentration to reduce injection volume. The defendants contend that methotrexate concentration is the common thread of all Asserted Claims and the single inventive concept flowing through the 662 Patent: *Apotex v Shire* at para 77. Since a number of 662 Patent claims are not limited by any treatment indication, the defendants submit the overarching inventive concept is methotrexate concentration "in the context" of subcutaneous administration.

[169] However, as noted above, the defendants argue that the obviousness analysis does not turn on a proper identification of the inventive concept because comparing the combination of claim elements to the state of the art leads to the same result.

[170] The plaintiffs submit the overarching inventive concept of the 662 Patent is threefold: (i) the use of methotrexate to treat inflammatory autoimmune diseases by subcutaneous injection,

(ii) where the methotrexate is present in concentrations higher than what were conventionally used to treat these diseases, and (iii) where the administration is by subcutaneous injection. Dr. Massarotti and Dr. Sinko opined that the skilled person would understand each Asserted Claim to have its own inventive concept that is similar to the overarching inventive concept, but unique.

[171] The plaintiffs state the Court should prefer Dr. Massarotti's and Dr. Sinko's opinions on the inventive concepts of the Asserted Claims. They contend Dr. Roth's and Dr. Rue's approach of limiting the inventive concept to concentration is a flawed approach that is inconsistent with Federal Court of Appeal jurisprudence. In *Bridgeview Manufacturing Inc v 931409 Alberta Ltd (Central Alberta Hay Centre)*, 2010 FCA 188 (at paragraph 51) [*Bridgeview*] and *Corlac Inc v Weatherford Canada Inc*, 2011 FCA 228 (at paragraph 69) [*Corlac*], the Federal Court of Appeal stated it is improper to break a combination of claim elements into parts and find that, because each element is known, the combination of elements is obvious. Furthermore, accepting the defendants' proposed inventive concept leads to claim redundancy. The plaintiffs say no expert opined that any Asserted Claims are redundant and redundancy should not be permitted at the inventive concept stage.

[172] While inventive concept is synonymous with the solution taught by the patent, the plaintiffs state the *Patent Act* requires that the "subject matter defined by a claim" not be obvious: *Patent Act*, s 28.3. They argue the defendants' experts' approach does not reflect the solution taught by the 662 Patent as defined by the subject matter of the claims. The plaintiffs point out that Dr. Rue agreed on cross-examination that the 662 Patent addresses a problem of patient compliance and teaches various ways to address it, including subcutaneous administration, ready-made syringes, single injections, self-administration, and injection volume

(or concentration). They say Dr. Roth's evidence on the inventive concept was confused and contradictory, and his cross-examination revealed that he struggled with an inventive concept that is limited to concentration and his opinion in fact aligns with those of Dr. Massarotti and Dr. Sinko that the inventive concept is not solely the concentration of methotrexate, but rather, includes the context that is provided by the essential elements of each Asserted Claim.

[173] The plaintiffs are correct that an obviousness analysis must focus on the specific patent claims at issue. The inventive concept that is important is the inventive concept of each claim, not a generalized inventive concept derived from the patent as a whole: *Apotex v Shire* at para 69. In this case, the parties' validity arguments focussed on the narrowest Asserted Claim and it is necessary to conduct the obviousness analysis for the narrowest claim. This is not a case where a non-obvious common or overarching inventive concept renders it unnecessary to consider narrowing limitations of dependent claims: *Apotex v Shire* at para 87.

[174] That said, identification of the inventive concept is distinct from claim construction. It is an exercise that is meant to help determine what, if anything, makes a claim inventive: *Apotex v Shire* at paras 74-77.

[175] Dr. Sinko equated the inventive concept with the elements of each Asserted Claim. His inventive concept of claims 1 and 18 simply restated every element of those claims. He considered the inventive concepts of the dependent Asserted Claims to be the same as the claim from which they depend with their added elements related to the methotrexate concentration, the pharmaceutically acceptable solvent, the disease being treated, the container for solution, or the injection device. Dr. Massarotti described the inventive concept of claim 1 as methotrexate for

treating IADs by subcutaneous injection at a concentration greater than 30 mg/ml, and stated the inventive concepts for the dependent claims were narrower because they include the additional elements specified in those claims.

[176] However, both Drs. Sinko and Massarotti agreed on cross-examination that for claim 1—which claims the use of methotrexate for the production of a subcutaneously administered medicament for the treatment of IADs wherein the methotrexate is present in a pharmaceutically acceptable solvent at a concentration of more than 30 mg/ml—the use of methotrexate for the production of a subcutaneously administered medicament for the treatment of IADs in a pharmaceutically acceptable solvent was already known prior to the 662 Patent.

[177] I disagree with the plaintiffs that Dr. Roth's evidence on inventive concept was confused or contradictory. He opined that every claim has a concentration element and he considered concentration to be the overall inventive concept. Although he noted that different claims have additional elements, in Dr. Roth's view the skilled person would not consider elements such as the use of methotrexate for IADs, dosing, packaging, or formats of presentation to be part of the inventive concept itself—and even if they were considered part of the inventive concept, these elements were no different from the state of the art. I accept Dr. Roth's evidence. I also accept Dr. Rue's similar evidence about formulation aspects of the Asserted Claims. He opined that aspects of the Asserted Claims apart from concentration would not be considered part of the inventive concept because those aspects were known.

[178] The plaintiffs' contend it is an error to limit the inventive concept to a single element. In my view, however, the plaintiffs mischaracterize the defendants' position and the defendants'

experts' opinions. Dr. Roth's and Dr. Rue's opinions on obviousness did not consider methotrexate concentration in isolation, divorced from the other elements of the Asserted Claims. As will be apparent in the sections below that address steps 3 and 4 of the obviousness analysis, the defendants and their experts did not approach obviousness as a simple exercise of identifying prior art methotrexate solutions that were more concentrated than 30 mg/ml—even though such solutions were known and used as medicines before 2006. Rather, the defendants and their experts considered whether the concentration of methotrexate, in the context of a subcutaneously administered medicament for treating IADs and other claim elements, would have been obvious to the skilled person. In my view, the parties' positions and the experts' opinions on inventive concept are far closer than the plaintiffs suggest.

[179] By 2006, it was known to the skilled person that methotrexate was used to treat IADs such as rheumatoid arthritis, including by administering a methotrexate solution by way of subcutaneous injection. In fact, this was conventional practice and part of the CGK. The skilled person knew, at the material times, that methotrexate was available in vials and pre-filled syringes containing a methotrexate solution that could be administered subcutaneously. The conventional practice used a 25 mg/ml methotrexate solution, whereas the 662 Patent states that the invention relates to solutions at concentrations above 25 mg/ml and each Asserted Claim requires a concentration above 30 mg/ml. It is the concentration aspect of each Asserted Claim that the skilled person would identify as the "what if anything that makes the claim inventive".

[180] There is no difference between the inventive concept as identified from reading the claims alone, compared to reading the claims with recourse to the specification: *Sanofi* at para 77; *Apotex v Shire* at paras 67-69. The 662 Patent identifies an injection volume problem with

methotrexate formulations in the prior art and presents the solution of increasing the concentration of methotrexate to reduce the volume of liquid. The second paragraph at page 7 of the patent reads:

> The medicaments provided by the present invention on the other hand contain highly concentrated solutions of the active substance methotrexate which results in a reduction of the amount of liquid to be administered with a certain weekly active substance dosage. For example, in the case of an especially preferred concentration of 50 mg/ml according to the present invention, it would be sufficient to administer a liquid volume of only 0.6 ml subcutaneously in order to keep with a weekly active substance dosage of 30 mg. It can be expected that this has a positive impact on patient compliance.

[181] As noted above, the narrowest of the Asserted Claims is Claim $10^{1-9}$:

> Use of methotrexate for the production of a subcutaneously administered medicament that is contained in a ready-made syringe for a single application and that is in a form suitable for patient self-administration, for the treatment of rheumatoid arthritis, wherein the methotrexate is present at a dosage of 5 to 40 mg in a pharmaceutically acceptable solvent selected from water, water for injection purposes, water comprising isotonization additives and sodium chloride, at a concentration of about 50 mg/ml.

[182] I have considered the claim limitations added by this claim and other Asserted Claims. I find that, apart from methotrexate concentration, the other claim elements do not impart an independent aspect of inventiveness. The other claim elements were already known, and they were known in combination. The limitations change the scope of the claim but they do not change its inventive concept.

[183] For claim $10^{1-9}$, the 662 Patent disclosure itself describes the claim elements, apart from concentration, as part of the prior art. The 662 Patent disclosure states methotrexate was being used at doses between 5.0 to 30.0 mg per week and up to 40 mg per week for antirheumatic

therapy, and methotrexate had improved bioavailability when it was administered parenterally. The 662 Patent disclosure also states, "ready-made syringes are well-known in the pharmaceutical field, in particular also in the treatment of rheumatoid arthritis with methotrexate." It states that ready-made syringes containing methotrexate solutions with concentrations of 7.5 mg/ml, 10.0 mg/ml, and 25 mg/ml in a pharmaceutically acceptable solvent were on the German market, although the 25 mg/ml syringe was not approved for subcutaneous application.

[184] Consequently, I find that the inventive concept of each claim is the concentration of methotrexate. Depending on the claim, it is expressed as a concentration that is 'more than 30 mg/ml', 'more than 30 mg/ml to 100 mg/ml', or 'about 50 mg/ml'. For claim $10^{1-9}$, the inventive concept is a methotrexate concentration of 'about 50 mg/ml'.

[185] I would note that the following are not part of the inventive concept of the Asserted Claims:

i. *Improved formulations or advantageous properties*: The 662 Patent describes the invention as medicaments or pharmaceutical solution formulations comprising methotrexate at a concentration of more than 25 mg/ml in a pharmaceutically acceptable solvent. The patent states concentrations of 25 to 150 mg/ml, 30 to 100 mg/ml, 40 to 80 mg/ml, and 50 to 75 mg/ml are preferred, and a concentration of about 50 mg/ml is especially preferred; however, it does not explain why these concentrations are preferred or especially preferred. Mr. Will did not overcome problems in formulating the claimed methotrexate solutions and the 662 Patent does not disclose any advantageous properties of such

formulations, such as improved bioavailability or reduced side effects when compared to existing formulations. These are not part of the inventive concept.

ii. *Identifying a problem that others did not identify*: The 662 Patent states that injecting a large amount of liquid under the skin may lead to reduced patient compliance. It states the medicaments of the invention contain highly concentrated solutions of methotrexate, which reduces the amount of liquid for administering a given dose and can be expected to have a positive impact on patient compliance. However, I agree with Dr. Roth that the impact of injection volume on discomfort or pain was not a new problem to be solved. I also agree with Dr. Roth that the example described in the 662 Patent of having to administer 3 ml of solution, which seems to refer to a 30 mg dose of methotrexate using a 10 mg/ml methotrexate solution, is exaggerated in the sense that, by 2006, a 30 mg dose of methotrexate could be delivered to a patient by injecting 1.2 ml of the 25 mg/ml solutions that were widely available and conventionally used to treat IAD patients by that time. Mr. Will did not identify a problem that others in the field did not appreciate, nor did he discover that injection volume can affect injection discomfort or that increasing concentration would allow the same methotrexate dose to be delivered in a smaller volume. These are not part of the inventive concept.

iii. *Combining claim elements*: I agree with the defendants that the 662 Patent is not a combination patent. The subject matter of the Asserted Claims does not derive inventiveness from non-obvious combinations of claim elements. Apart from

> concentration, the claim elements, in various combinations, were already part of the state of the art or even the CGK.

[186] I have identified the inventive concept from the skilled person's perspective by considering the claims in the context of the 662 Patent as a whole. I have done so having regard to the principle in *Bridgeview* and *Corlac* that it is improper to divide a combination of elements into its parts and find that, because each element is known, the combination of elements is obvious. Identifying methotrexate concentration as the inventive concept is not an exercise in improperly dividing a combination of elements into parts, or improperly considering a single claim element to the exclusion of other claim elements.

[187] While the concentration aspect of each claim is the inventive concept, the other claim elements provide context. All claims describe a methotrexate solution for subcutaneous administration and this is an important part of the relevant context for considering the inventive concept.

[188] Asserted Claims that depend on claim 1 (including claim $10^{1\text{-}9}$) include a treatment indication limitation. An important part of the relevant context for considering the inventive concept of this claim group includes that the methotrexate solution is for the treatment of IADs.

[189] Claim 18 and the Asserted Claims that depend on claim 18 do not include a treatment indication limitation. While the 662 Patent disclosure as a whole is more focussed on methotrexate solutions for the treatment of IADs, roughly half of the claims do not include a treatment indication and the skilled person would consider this to be intentional. Treatment

indication is also a main distinction between certain claims (for example, between claims 9 and 21). Even with recourse to the disclosure, the skilled person would not consider treatment of IADs to be part of the relevant context for the inventive concept of Asserted Claim 18 and its dependent claims.

[190] While the concentration aspect of each claim is the inventive concept, I also compared the combination of all claim elements to the state of the art for steps 3 and 4 in assessing whether the differences are obvious. The result is the same.

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

[191] In addition to the CGK, the state of the art includes references that were publicly available before the priority date: *Patent Act*, s 28.3; *Hospira Healthcare Corporation v Kennedy Trust for Rheumatology Research*, 2020 FCA 30 at paras 84-86 [*Hospira Healthcare*]. In this case, there is no dispute that the prior art references the parties and their experts relied on were publicly available before the priority date.

[192] As noted above in the section on CGK, the parties disagree on whether the skilled person would have considered products and literature relating to methotrexate in oncology to be part of the relevant state of the art relating to the 662 Patent.

[193] The defendants state that all publicly available prior art references form part of the state of the art: *Hospira Healthcare* at paras 84-86. The defendants state the skilled person would be informed by the state of the art about methotrexate, including products and literature related to cancer, which are at least relevant to questions of production, solubility, stability, concentration,

and suitable routes of administration. They contend the plaintiffs' experts improperly excluded relevant methotrexate references from their obviousness analysis.

[194] The plaintiffs argue that the skilled person does not include an oncologist and the 662 Patent is clearly directed to IADs. The plaintiffs contend the evidence shows that oncology and rheumatology are different diseases treated by different specialists who use methotrexate in very different ways. The skilled person would not have conflated the use of methotrexate in rheumatology and oncology, and would not rely on products or information about the use of methotrexate for the treatment of oncological disorders to inform them how to use methotrexate to treat IADs. The plaintiffs contend Dr. Rue's and Dr. Roth's evidence on what formed the state of the art is a hindsight analysis.

[195] For reasons similar to those above in relation to CGK, I find the literature and the information about available methotrexate products to be consistent with the defendants' position. The skilled person would not have excluded methotrexate literature or products related to oncology from the relevant state of the art. The pre-2006 literature often discusses cancer and IAD treatment in the same document, the same product was often used for both indications, and the labels and pharmaceutical reference texts describing available methotrexate products often discussed both indications.

[196] The defendants submit the skilled person would have known at least the following from the state of the art: (i) pre-filled syringes containing a 25 mg/ml methotrexate solution were available ready-made or prepared at clinical pharmacies, and used for patient self-administration by subcutaneous injection to treat IADs (Jansen 1999); (ii) pre-filled syringes containing

methotrexate up to a concentration of 50 mg/ml in a water-based solution were known to be stable (Wright 1988); (iii) methotrexate injectable solutions were available in vials at concentrations of 25 mg/ml and 50 mg/ml, and specifically indicated for intramuscular and intravenous administration (Wyeth); (iv) methotrexate injectable solutions were available at a concentration of 100 mg/ml, and specifically indicated for intramuscular and intravenous administration to treat neoplastic diseases (Hospira); (v) doses of methotrexate of up to 30 mg per week were used to treat psoriasis (Goodman and Gilman's); (vi) doses of methotrexate of up to 40 mg per week, administered subcutaneously, were used to treat rheumatoid arthritis (Hoekstra 2004; Alsufyani 2004); (vii) subcutaneous injection volumes should generally be 1 ml or less (Contemporary Pharmaceutics; Aulton's); and (viii) subcutaneous injection pain increased significantly when injection volume increased from 0.5 to 1.0 ml (Jørgensen 1996).

[197] The defendants also submit that, based on the literature, the skilled person would readily infer that: methotrexate was soluble in water and sodium chloride up to at least 100 mg/ml; methotrexate solutions up to 100 mg/ml had an acceptable shelf life for pharmaceutical use; and a good target for subcutaneous injection volume is 0.5 ml.

[198] The defendants argue the only identifiable difference between the inventive concept and the state of the art for claim 3 and its dependent claims is a specific and express link between 50 mg/ml concentration of methotrexate *and* subcutaneous administration *and* treatment of rheumatoid arthritis.

[199] The plaintiffs submit the state of the art as of 2006 was that, when methotrexate was used subcutaneously to treat inflammatory autoimmune diseases, the concentration was 25 mg/ml and the doses ranged from 7.5 to 25 mg per week. In addition, the skilled person would have known that vials containing methotrexate at a concentration of 25 mg/ml were widely used to prepare syringes for subcutaneous administration. The plaintiffs argue that the difference between the inventive concept of claim 1 and the state of the art is three distinct elements in combination: (i) using methotrexate concentrations greater than 30 mg/ml, (ii) to treat autoimmune diseases, (iii) by subcutaneous injection.

[200] In my view, the defendants' account of what the skilled person would have understood to be part of the state of the art is accurate. Much of this information, at least at a general level, would have been CGK. The defendants' position is supported by their experts' evidence, which I accept, and by the pre-July 2006 literature.

[201] The defendants correctly state that this is not a combination case, because, apart from a 50 mg/ml concentration, the other claim elements were CGK in various combinations. The skilled person would not have to combine knowledge from different fields or combine knowledge from different prior art references in the same field.

[202] The plaintiffs equate the state of the art with the conventional practice for treating rheumatoid arthritis and other IADs. I would agree that the conventional practice presents a reference point for considering the question of obviousness—that is, whether differences between the conventional practice and the inventive concept of claim $10^{1\text{-}9}$ was obvious. However, the state of the art in 2006 was not limited to the conventional practice and other

aspects of the state of the art inform the assessment of whether the gap between the conventional practice and the claimed invention was inventive. These aspects include, for example, the information known in the art about pre-filled syringes, methotrexate solutions at concentrations above 25 mg/ml that were commercially available, and the relationship between injection volume and patient discomfort.

[203] I will now turn to step 4 of the obviousness analysis, whether the differences between the state of the art and the invention would have been obvious to the skilled person or required any degree of inventiveness.

(6) Step 4: Are the Differences Obvious?

[204] The defendants contend the skilled person could have bridged the differences between the state of the art and the inventive concept using only their CGK and elements of the prior art they could have found upon a reasonably diligent search: *Ciba Specialty Chemicals Water Treatments Limited v SNF Inc*, 2017 FCA 225 at paras 68, 92-95 [*Ciba*]; *Hoffmann-La Roche Ltd v Apotex Inc*, 2013 FC 718 at paras 317-318. Bridging the gap was obvious because a 50 mg/ml concentration methotrexate solution was in the state of the art and everything else was CGK.

[205] The defendants submit there is no need to assess whether the claimed invention was obvious to try if the Court finds no inventiveness was required to bridge the gap between the state of the art and the inventive concept: *Ciba* at para 96; *Bristol-Myers Squibb Canada Co v Teva Canada Limited*, 2017 FCA 76 at paras 76-77 [*Bristol-Myers Squibb*]. However, increasing concentration was also obvious to try because it was simply a logical progression: *Janssen Inc v Apotex Inc*, 2021 FC 7 at para 186.

[206] The defendants say the *Beloit* question is not dispositive and in any event, the answer is the same as in *Bauer*—a design that was never adopted because it was not profitable to do so does not render it any less obvious: *Bauer Hockey Ltd v Sport Maska Inc (CCM Hockey)*, 2020 FC 624 at paras 147, 162-165, aff'd 2021 FCA 166. The defendants say Mr. Will, who does not have a background in science, did not contribute new knowledge to the field or address a new problem. Instead, he identified a market gap based on discussions with physicians and made a commercial decision to market a 50 mg/ml methotrexate product. There was little commercial incentive for most companies to invest in new products for a 50-year-old genericized drug, but medac was able to develop a 50 mg/ml product as a line extension of existing products with low investment.

[207] The plaintiffs contend Dr. Roth's and Dr. Rue's evidence is fundamentally flawed. Drs. Roth and Rue assumed the skilled person would be aware of a problem with existing methotrexate products and would have asked a formulator to prepare a new formulation, and they conducted their obviousness analysis by asking whether it would be straightforward to create the claimed methotrexate formulations. The plaintiffs say there is nothing in the prior art or CGK establishing that the skilled person would operate from the same assumption and the defendants' approach to obviousness suffers from the same fatal flaws as the obviousness argument advanced and rejected in *Janssen Inc v Actavis Pharma Company*, 2016 FC 1361 [*Janssen v Actavis*]. At best, the defendants' position is that *if* the skilled person were presented with the problem of injection site pain, it would have been obvious to increase concentration. However, Mr. Will was not asked to develop a new methotrexate formulation, Drs. Jansen and Janssen testified there were no issues with the existing 25 mg/ml methotrexate formulation, and

the defendants did not lead fact evidence to prove the assumptions upon which their experts' opinions were based: *R v J-LJ*, 2000 SCC 51 at para 59; *Janssen v Actavis* at paras 48-49.

[208] As noted above, the plaintiffs caution that hindsight must not creep into an obviousness analysis and they rely on the question posed in *Beloit* (at page 8) to refute obviousness. The plaintiffs submit the Court should accept Dr. Massarotti's unchallenged evidence that the prior art did not motivate the skilled person to create a new methotrexate formulation to address injection site pain. Furthermore, real world formulators did not develop the invention—companies that were producing methotrexate products at the time did not develop a 50 mg/ml methotrexate formulation and Drs. Jansen and Janssen, who were working in the field, did not consider raising concentration above 25 mg/ml, much less creating a new methotrexate formulation. Where there is a problem only the claimed inventor is trying to solve and no one else has reason to address, it may be more likely that the solution required inventive ingenuity: *Novopharm Ltd v Janssen-Ortho Inc*, 2007 FCA 217 at para 25 [*Novopharm*].

[209] The plaintiffs urge the Court to reject the defendants' experts' opinions as impermissible hindsight. They contend the Court should prefer Dr. Massarotti's and Dr. Sinko's evidence explaining the differences between the state of the art and the inventive concept of each Asserted Claim. It was not obvious for the skilled person to create a new methotrexate formulation because there was no reason to depart from the conventional practice that used a 25 mg/ml methotrexate solution, injection site discomfort would not have motivated the skilled person, and concerns about side effects would have dissuaded the skilled person from considering higher concentrations.

[210] I disagree with the plaintiffs that Dr. Roth's and Dr. Rue's opinions on obviousness suffer from the same flaw as the obviousness argument in *Janssen v Actavis*. In that case, the inventor discovered that an underlying problem with the pharmaceutical compound in question, methylphenidate, was caused by acute tolerance, and the inventor developed a sustained-ascending dosage form to address acute tolerance. Consequently, the Court was critical of expert evidence that assumed acute tolerance was a known problem, assumed that ascending release formula was the solution, and opined that if a skilled formulator had been asked to make a sustained-ascending dosage form he or she could have done so using routine techniques. The opinions were impermissible hindsight because there was nothing in the prior art or CGK that would have allowed the skilled person to operate from an assumption that acute tolerance to methylphenidate was a problem to be solved. The Court determined the invention was not obvious to try because those in the field doubted that acute tolerance was a problem and further, using a sustained-ascending dosage form of methylphenidate had never before been tried as a means of addressing acute tolerance.

[211] *Janssen v Actavis* is distinguishable. In this case, Drs. Roth and Rue did not base their opinions on unproven assumptions. They were asked to consider an alternative obviousness scenario, and for that scenario they assumed that the identification of an injection pain problem or the reduction of injection pain was part of the inventive concept for the Asserted Claims. In view of my findings on the inventive concept, the alternative obviousness opinions are not relevant. For the reasons explained above, the invention of the 662 Patent did not lie in identifying an injection pain problem or in identifying a volume-reducing solution to injection pain. The skilled person already knew that injections can be painful and it was CGK that the

volume of solution injected into muscle or injected under the skin is a factor that could influence injection pain. These were not part of the inventive concept.

[212] I disagree with the plaintiffs that the defendants' experts' opinions were based on hindsight. I also disagree with their position regarding the motivation to pursue the invention and the *Beloit* question.

[213] The plaintiffs point to the Federal Court of Appeal's statement about motivation in *Novopharm* at para 25:

[…]

> 5. The motivation in existence at the time the alleged invention to solve a recognized problem
>
> "Motivation" in this context may mean the reason why the claimed inventor made the claimed invention, or it may mean the reason why one might reasonably expect the hypothetical person of ordinary skill in the art to combine elements of the prior art to come up with the claimed invention. If within the relevant field there is a specific problem that everyone in the field is trying to solve (a general motivation), it may be more likely that the solution, once found, required inventive ingenuity. On the other hand, if there is a problem that only the claimed inventor is trying to solve (a unique or personal motivation), and no one else has a reason to address that problem, it may be more likely that the solution required inventive ingenuity. However, if commonplace thought and techniques can come up with a solution, there may be a reduced possibility that the solution required inventive ingenuity.

[…]

[214] This is not a case where motivation makes it more likely that the solution required inventive ingenuity, because the problem was one that only the claimed inventor was trying to solve. If anything, motivation favours the defendants' position. In this case, the level of motivation for solving the problem provides an answer to the *Beloit* question. Furthermore, the

solution of the 662 Patent was reached by commonplace thought and techniques, namely, an understanding that the same dose of methotrexate can be delivered to a patient in less solvent using a more concentrated solution, and that achieving a practical injection volume for any given methotrexate dose depends on concentration.

[215] Mr. Will's motivation for making the claimed invention came from discussions with rheumatologists who were using medac's methotrexate formulations to treat IADs by subcutaneous injection. They reported a volume problem. Mr. Will testified that the rheumatologists told him they had to administer the product in three or four areas in order to get all of the solution under the patient's skin. This was the problem referred to in the 662 Patent. The patent disclosure states that patients treated with existing methotrexate preparations showed a disapproving attitude that was "due to the problem of having to inject the required relatively large amount of active substance solution (e.g. up to 3 ml in the case of a certain dosage)".

[216] A 25 mg dose of methotrexate required administration of 2.5 ml of medac's 10 mg/ml product. Using the 25 mg/ml solution that was conventionally used by 2006 had already "solved" the volume problem with a 10 mg/ml solution because the vast majority of IAD patients using subcutaneously administered methotrexate could receive their weekly dose with one injection of a reasonably small volume of 1 ml.

[217] Some patients receiving conventional doses with a 25 mg/ml solution would have required an injection that delivered more than the target 0.5 ml volume, and patients on higher doses may have required an injection that delivered more than 1 ml, which would have required multiple injections using a 1 ml syringe. However, injection volume was not a pressing problem

or one that others in the field were trying to solve. Dr. Roth opined that the issue of injection pain and injection volume was not a big problem since the maximum methotrexate dose for the vast majority of IAD patients was 25 mg, and so injection volumes using the 25 mg/ml solution rarely exceeded 1 ml. Consequently, he did not believe a skilled clinician would view the absence of a methotrexate 50 mg/ml product specifically approved for rheumatoid arthritis as indicative of a clinical problem that had not been solved.

[218] I accept Dr. Roth's evidence and prefer it to that of Dr. Massarotti, whose opinion was, in my view, overly influenced by a desire to avoid any deviation from a conventional practice using a 25 mg/ml vial of methotrexate solution, and any change that would require "rejiggering" of the syringe used or the instructions given to the nurse, patient, or other person administering the injection.

[219] In any event, on the question of motivation, I find Dr. Massarotti's views are actually fairly close to those of Dr. Roth. Dr. Massarotti testified that, by 2006, the problem of having to inject up to 3 ml was no longer a problem for the conventional dose range because a 25 mg/ml methotrexate solution was available, and the conventional practice of administering a 25 mg/ml solution using a 1 ml syringe worked well the majority of the time. In rare situations where the prescribed dose exceeded 25 mg, Dr. Massarotti's view was that conventional practice was to use a larger syringe or split the dose into two injections, but she conceded on cross-examination that it would be preferable to give as few injections as possible. Dr. Massarotti testified that, even today, she uses the 25 mg/ml solution rather than medac's 50 mg/ml product to treat rheumatoid arthritis and it was her view that the skilled person would do the same. The evidence demonstrates that injection volume was not a significant problem with the 25 mg/ml solution.

[220] Concerns about side effects or toxicity would not have dissuaded the skilled person from considering higher concentrations. As noted in the section on CGK, the literature indicates that methotrexate's side effects and toxicity may be affected by dose, frequency of administration (the body has less time to rebound if methotrexate is given daily rather than weekly), or prolonged use, but in my view it does not support that methotrexate's side effects and toxicity were considered to be concentration-dependent.

[221] Dr. Massarotti stated in her report that concentration affects dose-related toxicity because there is more room for error:

> While "dose" (the amount of methotrexate) and "concentration" (the amount of methotrexate in a given volume) are different, and the same dose can be administered using two different concentrations (25 mg can be administered by injecting 1 ml of 25 mg/ml solution or 0.5 ml of 50 mg/ml solution), there is a significant reason why it would not be obvious to the [skilled person] to use a concentration higher than 25 mg/ml. At higher concentrations, small changes in volume result in larger changes in dose. For example, at 25 mg/ml, a change in volume of 0.1 ml results in a change in dose of 2.5 mg, whereas the same change in volume at 50 mg/ml results in a change of dose of 5 mg. These changes are particularly significant to the [skilled person] because of the increased toxicity of methotrexate at higher doses.

[222] I am not persuaded that this was a reason the claimed invention would not have been obvious to the skilled person. Administering methotrexate using a 25 mg/ml vial and a 1 ml capacity syringe does not provide "dose protection" except in the sense that a 25 mg dose fills a 1 ml syringe. Using a 25 mg/ml solution and 1 ml syringe does not prevent mistaken daily rather than weekly administration (something noted in the pre-2006 literature), it does not protect patients prescribed a dose below 25 mg from drawing a higher dose using a 1 ml syringe, and it is unclear to me why a skilled person would necessarily use a 1 ml capacity syringe to draw up a

50 mg/ml solution. Moreover, as Dr. Massarotti acknowledged on cross-examination, pre-filled or commercial ready-made syringes, which were already being used for methotrexate injections prior to July 2006, contain a specific dose.

[223] Drs. Roth and Rue provided credible, supported opinions explaining why the skilled person would consider the differences between the state of the art and the inventive concept to be obvious. I accept their evidence that:

i. Formulating higher concentration products would be routine for the skilled formulator and it was already known that a higher concentration of methotrexate could be used in a commercial product. Methotrexate products available before 2006 included: a 50 mg/ml injectable product supplied by Wyeth as a 1 g vial, which was described in the same product label as a 25 mg/ml supplied as a 20 mg vial, and; a 100 mg/ml injectable product supplied by Hospira.

ii. Methotrexate liquid formulations for intramuscular and subcutaneous injection were considered to be interchangeable. The subcutaneous route of administration was well known and the skilled person would have prescribed methotrexate formulations via subcutaneous administration, even if they were not specifically indicated for that route of administration.

iii. The skilled person would not consider there to be a significant reason why a higher concentration methotrexate solution could not be administered to patients subcutaneously to treat IADs. Methotrexate was not considered a major irritant when used in an injectable form, and as noted above, the literature does not support that methotrexate's side effects and toxicity were considered to be concentration-dependent. Product labels did not include warnings or distinguish

between treatment indications or routes of administration for lower and higher concentration solutions.

iv. The skilled person considered 0.5 ml to be a good target volume.

[224] I accept the opinions of Drs. Roth and Rue and agree with them that the skilled person would not view changing concentration as a big step. Mr. Will did not create a new methotrexate formulation, and methotrexate formulations for parental administration at concentrations up to 100 mg/ml were already commercially available as medicines for human use.

[225] The skilled person possesses no imagination or inventiveness, but they pursue reasonable and logical enquiries and they can make deductions based on the information available. Understanding the volume of solution at a given concentration needed to deliver a desired dose was a matter of routine. In fact, the 662 Patent itself states (at page 6, 2nd paragraph), "The volume of the liquid necessary to provide the desired dose, which has to be contained in the injection device for a single application, depends on the concentration of the active substance solution and is obvious to the person skilled in the art."

[226] Comparing the combination of elements in claim $10^{1\text{-}9}$ to the state of the art leads me to the same result. Each of the elements of claim $10^{1\text{-}9}$ in combination was a way to treat patients with rheumatoid arthritis before 2006, except that the conventional practice used a 25 mg/ml methotrexate solution instead of the claimed 50 mg/ml solution. The "gap" between the combination of claim elements for claim $10^{1\text{-}9}$ and the state of the art is the concentration. For

the same reasons explained above, the skilled person would have bridged the differences between the state of the art and the elements claim $10^{1-9}$ without inventive ingenuity.

[227] As the differences between the inventive concept and the state of the art would have been obvious to the skilled person as of 2006, there is no need to assess whether the claimed invention was obvious to try: *Ciba* at para 96; *Bristol-Myers Squibb* at paras 76-77.

[228] The narrowest Asserted Claim, incorporating every limitation of its dependent claims, is obvious. No other element of other Asserted Claims imparts inventiveness. I find the defendants have established that each of the Asserted Claims is obvious.

D. *Other invalidity grounds*

(1) Anticipation

[229] The subject matter defined by a patent claim must not have been disclosed before the claim date in such a manner that it became available to the public in Canada or elsewhere: *Patent Act*, s 28.2(1)(b). Anticipation requires that the claimed subject matter be disclosed and enabled: *Sanofi* at para 26.

[230] The defendants rely on two prior art references for anticipation: they contend Wyeth anticipates claims 1-6 and US 504 anticipates claims 1, 2, 4, 5, and 6. The defendants argue Wyeth discloses all elements of claims 1-6 (use of methotrexate to treat IADs, subcutaneous administration, pharmaceutically acceptable solvents, and a 50 mg/ml concentration) and US 504 discloses all elements of claims 1-2 and 4-6 (use of methotrexate to treat IADs, subcutaneous administration, pharmaceutically acceptable solvents, and concentrations up to 40 mg/ml).

[231] The plaintiffs contend the anticipation allegations are irrelevant because the defendants concede infringement of all Asserted Claims, but the anticipation allegations only affect a subset of them. In any event, the plaintiffs submit that claims 1-6 are not anticipated by Wyeth and/or US 504, including because Wyeth and US 504 could be practiced in ways that would not necessarily infringe any Asserted Claims.

[232] In view of the defendants' concession that they would infringe all Asserted Claims, I agree with the plaintiffs that no purpose would be served by deciding whether claims 1-6 are invalid for anticipation.

(2) Ambiguity

(a) *The parties' submissions*

[233] The defendants submit that claims 3, 20, and their dependent claims do not define the claimed monopoly "distinctly and in explicit terms": *Patent Act*, s 27(4). Claims must not be flexible; they must be clear and precise: *Free World Trust* at para 14. The defendants assert that the term 'about 50 mg/ml' in claims 3 and 20 does not provide an unambiguous boundary demarcating the monopoly because the 662 Patent does not define the term or provide a way for the skilled person to tell whether a concentration falls within it.

[234] The defendants rely on Dr. Rue's opinion that 'about' does not have a precise definition in the art. While the skilled person would know that 'about 50 mg/ml' includes 50 mg/ml, the numerical range covered by the claim is not defined in the 662 Patent and it cannot be ascertained. At best, according to Dr. Rue, 'about' means 'approximately' and is not a term of art having a more precise meaning.

[235] The defendants state Dr. Sinko's proposed range of ±10% is arbitrary. His evidence was that this range is a good starting point in view of the United States Pharmacopeia (USP). The defendants contend the USP cannot assist in construing the claims because the USP was not referenced in the 662 Patent, the ±10% rule appears in a section on tests and assays and claims 3 and 20 do not cover a test or assay, and the USP rules do not apply to the general literature.

[236] The defendants say Dr. Sinko's evidence on cross-examination demonstrates that 'about 50 mg/ml' is flexible and the skilled person would not know its boundaries. He used language like "a little bit more or a little bit less" than 50 mg/ml. When asked if 56 mg/ml would fall outside the claims, he answered it was "starting to get up there".

[237] The plaintiffs contend ambiguity is a last resort, rarely, if ever, to be used: *Alcon Canada Inc v Cobalt Pharmaceuticals Company*, 2014 FC 149 at para 232 [*Alcon*]. If a skilled person can construe a claim, it cannot be ambiguous: *Western Oilfield Equipment Rentals Ltd v M-I LLC*, 2021 FCA 24 at para 121. The plaintiffs argue Dr. Rue was the only expert who had difficulty with the term 'about 50 mg/ml'—despite having construed similar claims in foreign litigation without identifying any issue. He also changed the basis for his ambiguity opinion, stating in his report that the word 'about' is not used by skilled formulators and would have no meaning when used with concentration, and stating on cross-examination that 'about 50 mg/ml' is ambiguous because it does not define a precise numerical range or limit. The plaintiffs argue Dr. Rue's evidence on the issue of ambiguity is not credible and his construction of the claim term 'about 50 mg/ml' was influenced by the legal issues advanced by the defendants rather than his own understanding of the term or the skilled person's understanding of it.

[238] The plaintiffs argue a claim is not ambiguous just because its scope could be defined with greater precision: *Omark Industries (1960) Ltd v Gouger Saw Chain Co et al* (1964), 1 Ex CR 457 at 510, 1964 CanLII 1086; *Burton Parsons Chemicals, Inc v Hewlett-Packard (Canada) Ltd*, [1976] 1 SCR 555 at 565-566, 54 DLR (3d) 711 [*Burton Parsons*]; *Deeproot Green Infrastructure, LLC v Greenblue Urban North America Inc*, 2021 FC 501 at paras 252-253. They submit this Court has rejected the argument that use of 'about' in specifying claimed dosage ranges renders the claims ambiguous: *Bayer Inc v Cobolt Pharmaceuticals Company*, 2013 FC 1061 at paras 103-106 [*Cobolt*]. The plaintiffs rely on Dr. Sinko's opinion that a skilled person would have no difficulty understanding 'about 50 mg/ml' in the context of the claims and, if the skilled person required clarification of the scope of the claim, they would look to a reference text such as the USP to confirm an appropriate range to be within 10%. The plaintiffs contend Dr. Sinko's approach is consistent with previous decisions of this Court: *Sanofi-Aventis Canada Inc v Ratiopharm Inc*, 2010 FC 230 at paras 39-41; *Valeant Canada LP/Valeant Canada SEC v Ranbaxy Pharmaceuticals Canada Inc*, 2018 FC 847 at paras 83-103; *Cobolt* at paras 103-106; *Apotex Inc v Syntex Pharmaceuticals International Ltd* (1999), 166 FTR 161 at para 45, 1 CPR (4th) 22.

(b) *Analysis*

[239] I will first address the plaintiffs' criticisms of Dr. Rue's evidence.

[240] I disagree with the plaintiffs that the basis for Dr. Rue's opinion on ambiguity changed on cross-examination. In his report, Dr. Rue stated the skilled formulator would have no precise understanding of the boundary for the term 'about 50 mg/ml' because the 662 Patent disclosure and claims give no indication of the acceptable range for the term 'about', and it is unclear what

range of concentrations should fall within this term. In his view, ‘about 50 mg/ml’ differs from ‘50 mg/ml’, which the skilled formulator would understand as a specific concentration that can be measured within experimental limits of error. The answers Dr. Rue gave on cross-examination are consistent with the opinion expressed in his report. On cross-examination, Dr. Rue explained that, while ‘about’ means ‘approximately’, these words do not define limits in the sense of defining what the claims at issue do and do not cover.

[241] I also disagree with the plaintiffs that Dr. Rue’s difficulty with ‘about’ was more influenced more by the legal issues or that his failure to identify an ambiguity issue in foreign proceedings tarnished his credibility. Dr. Rue readily conceded that he did not identify a similar issue in construing ‘about 50 mg/ml’ in the EWHC proceeding between Accord and medac. He testified that he missed ambiguity in the EWHC proceeding, he was not asked to explain what ‘about’ meant, the precise scope of the claims was not discussed, and he does not know why. Dr. Rue testified that, had he been asked, he would have been unable to define the range then, just as he is unable to define the range now. Dr. Rue’s explanation struck me as a candid and reasonable one. Expert witnesses are guided by the mandates provided by counsel and the mandate Dr. Rue was given in this proceeding made him think about something he had not thought about before. Nothing about Dr. Rue’s testimony led me to believe that his opinion was merely an echo of the defendants’ position.

[242] In summary, I reject the plaintiffs’ arguments about Dr. Rue’s credibility. Counsel’s cross-examination was exacting and Dr. Rue did not capitulate, but his answers remained impartial and objective. There is no reason to doubt that Dr. Rue gave the Court his truthful and reasonably held opinion.

[243] That said, the defendants bear the burden of establishing that claim 3 and 20 (and their dependent claims) are invalid for ambiguity. In my view, they have not met their burden. The evidence in this case does not satisfy me that a skilled person cannot ascertain the boundaries of claims 3 and 20 because 'about 50 mg/ml' is incapable of a sufficiently precise meaning that is fair to both the patentee and the public.

[244] Claims are to be understood from the perspective of the skilled person with a mind willing to understand, and claims will not be invalidated simply because they are not a model of concision and lucidity; if a claim can be understood using grammatical rules and common sense, it cannot be ambiguous: *Alcon* at para 232, citing *Letourneau v Clearbrook Iron Works Ltd*, 2005 FC 1229 at para 37.

[245] 'About' has an ordinary grammatical meaning. It conveys an approximation or, in Dr. Rue's words, it is synonymous with 'close to'. The evidence in this case demonstrates that the scientific literature in the field at the material time frequently used 'about' in association with various measurements, and it does not appear that use of the word was an impediment to comprehension.

[246] Dr. Rue agreed that 'about' can be used in the sense of 'approximately'; however, in his opinion, 'about' does not define a range and so the skilled person would not understand the boundary of claims 3 and 20. Put another way, at one point Dr. Rue stated, "I can't tell you what it means in terms of the width" of the claim.

[247] I agree with the plaintiffs that the lack of an exact numerical range does not, on its own, render a claim ambiguous. Some level of imprecision is permitted: *Burton Parsons* at 565-566. Even without the word 'about' in claims 3 and 20, some variation on either side of 50 mg/ml would be expected. As noted above, Dr. Rue's opinion is that a skilled formulator would be able to understand '50 mg/ml' because it is a specific number that can be measured within experimental limits. For example, if a hypothetical measurement apparatus were precise to ±1%, the skilled formulator would know that a methotrexate solution with a measured concentration within those experimental margins would be "equal" to 50 mg/ml for the purposes of the claim. However, Dr. Rue states that the skilled person's task in that situation is different from determining whether a concentration of 49 mg/ml falls within the claim term 'about 50 mg/ml', and the 662 Patent does not refer to ranges of acceptable error, bioequivalence criteria, experimental apparatus, or any other data that would provide guidance on the meaning of 'about'.

[248] I am not persuaded that the word 'about' changes the nature of the claim from the skilled person's perspective. Dr. Rue does not give a compelling reason why the skilled person would see 'about 50 mg/ml' as being materially different from '50 mg/ml' with a margin. Dr. Sinko stated that even exactly 50 mg/ml could be ±10%, "it's just something in [the skilled person's] understanding of the way our field works".

[249] However, the defendants' position on ambiguity does have merit in that no expert offered compelling evidence of what the skilled person would expect the boundaries for claims 3 and 20 to be. While there is no doubt that 50 mg/ml falls within 'about 50 mg/ml', no expert provided a

definitive opinion on the concentrations on either side of 50 mg/ml that the skilled person would consider to fall within the scope of the claims.

[250] Dr. Sinko's report states the skilled person would "simply look to a reference text" such as the USP to confirm the appropriate range, but he wavered on cross-examination. He began by saying ±10% was a "starting point", then reluctantly committed to ±10% after further questioning:

> Q. You would understand, from the perspective of a skilled person reading the claims, that skilled person would have to know whether they're inside or outside that boundary so as not to infringe the claim; correct?
>
> A. That's correct.
>
> Q. Okay. So, in your view, then, is it correct that someone who creates a 56 mgs per ml methotrexate [solution] would fall outside of Claim 3?
>
> A. Well, like I said, you know, someone's going to have a rough idea of, based on their experiences. And so would 56? Yeah, you're starting to get up there. Would it fall outside? I would say based on the general rule of thumb, given this type of language in this type of circumstance and context, that would probably fall outside.
>
> Q. Would probably fall outside or would to fall outside. We are to have a demarcation line?
>
> A. Yeah, yeah. I understand. I would say it would fall outside, then.
>
> Q. So your view, then, to confirm your opinion is that this demarcation line is plus/minus 10 percent or, in other words, 45 to 55 mgs per ml?
>
> A. Like I said, yeah. I think, for this type of circumstance, that would be okay.

[251] I do not find Dr. Sinko's evidence on this point convincing. I do not see why ±10% is the proper limit for claims 3 and 20 of the 662 Patent, particularly since the patent does not explain

why certain concentration ranges are preferred or why ‘about 50 mg/ml’ is especially preferred. It is not clear me, based on the evidence, that the skilled person would consider ±10% to define the boundary for claims 3 and 20.

[252] However, in my view, it is unnecessary for this Court to reach a specific finding on the skilled person’s understanding of the boundary for claims 3 and 20. It is unnecessary to do so in order to reject the ambiguity ground and nothing else in the case turns on it. The defendants concede infringement of all Asserted Claims, including claims 3, 20, and their dependent claims, and the parties and their experts have addressed all other invalidity grounds without the need to define the boundary of Asserted Claims that include the term ‘about 50 mg/ml’.

[253] As noted above, I reject the ambiguity ground on the basis that the defendants have not met their burden. The defendants have not persuaded me that the skilled person would be unable to define ‘about 50 mg/ml’ with sufficient precision so as to be fair to both the patentee and the public.

[254] A patent claim should not be invalidated for ambiguity if the patent specification can assist in construing the claim. Dr. Rue states he considered the 662 Patent specification. In his view, the 662 Patent does not provide any definition or other guidance for the term ‘about’, and “[n]either the claims nor the disclosure give any indication of the acceptable range for the term ‘about’”. Dr. Rue noted that the 662 Patent does not refer to ranges of acceptable error, bioequivalence criteria, experimental apparatus, or any other data that would provide guidance on the meaning of ‘about’.

[255] In my view, the type of information Dr. Rue was looking for was unduly narrow. For example, on cross-examination Dr. Sinko noted that the examples in the 662 Patent for preparing 50 mg/ml methotrexate formulations resulted in concentrations below 50 mg/ml. Dr. Sinko's evidence was that preparing methotrexate solutions according to the examples in the 662 Patent results in "something like 47 or 48" mg/ml solutions. It seems to me that this information—instructions for preparing a 50 mg/ml methotrexate solution that actually result in a 47 mg/ml or 48 mg/ml methotrexate solution—would be of assistance in understanding what the inventor meant by 'about 50 mg/ml' in the claims.

[256] In conclusion, the defendants have not established that 'about' is incapable of understanding, nor have they established that 'about 50 mg/ml' cannot provide an unambiguous boundary defining the scope of the monopoly. The defendants have not established that claims 3, 20, and their dependent claims are invalid for ambiguity because the skilled person, with the assistance of the specification and a mind willing to understand, would be unable to construe the claim term 'about 50 mg/ml'.

(3) Utility, Insufficiency, Overbreadth

[257] A patent claim may be invalid if:

i. the utility of a claimed invention was not demonstrated or soundly predicted based on the information and expertise available at the material date, which is no later than the filing date: *Patent Act*, s 2; *Apotex Inc v Wellcome Foundation Ltd*, 2002 SCC 77 at para 56; *Apotex Inc v Janssen Inc*, 2021 FCA 45 at para 37;

ii. the patent specification provides insufficient information to enable the skilled person to practice the invention: *Patent Act*, s 27(3); *Teva Canada Ltd v Pfizer*

*Canada Inc*, 2012 SCC 60 at para 51 [*Teva v Pfizer*], citing *Pioneer Hi-Bred Ltd v Canada (Commissioner of Patents)*, [1989] 1 SCR 1623 at 1637-1638, 60 DLR (4th) 223; or

iii. the subject matter of the claim exceeds the invention that was made or exceeds the invention disclosed in the specification: *Pfizer Canada Inc v Canada (Minister of Health) (FC)*, 2008 FC 11 at paras 45-46; *Eli Lilly Canada Inc v Apotex Inc*, 2018 FC 736 at para 131.

[258] I will address utility, insufficiency, and overbreadth to the extent the defendants' allegations are relevant to claim $10^{1\text{-}9}$.

[259] medac conducted three studies prior to the Canadian filing date. A first study in rabbits examined local tolerance of subcutaneously administered methotrexate between a commercially available 10 mg/ml formulation and a 50 mg/ml formulation following a single injection of 1 ml or 2 ml. A second study in rabbits examined local tolerance of a 50 mg/ml methotrexate formulation after a single intravenous, intra-arterial, intramuscular, paravenous, and subcutaneous injection, with the injection sites studied at various point of time up to 14 days post-administration. A third study with healthy male subjects, and having a primary objective of assessing relative bioavailability, compared a 15 mg dose of 10 mg/ml and 50 mg/ml methotrexate solution administered by subcutaneous and intramuscular injection.

[260] The defendants contend that medac's studies did not demonstrate utility across the full scope of the Asserted Claims. In this regard, they argue that medac's studies can only demonstrate utility at the single concentration and dose tested, and the utility of other covered

concentrations and doses must be based on sound prediction. The defendants also argue medac did not demonstrate utility for treatment indications, and the utility of methotrexate for certain treatment indications covered by the Asserted Claims were not within the CGK. The defendants state utility was not soundly predicted because, if this Court were to accept medac's experts' concerns about safety and toxicity: (i) the 662 Patent disclosed no data to support a sound prediction; and (ii) the alleged concerns would preclude a sound prediction for any concentrations or doses apart from those tested.

[261] The defendants' allegations of insufficiency and overbreadth are similar. On insufficiency, the defendants state that if the Court accepts that the skilled person would have been concerned about toxicity and side effects of a concentrated methotrexate solution, the skilled person would not be able to make the same successful use of the invention as medac because no safety data were disclosed in the 662 Patent: *Patent Act*, s 27(3); *Teva v Pfizer* at paras 50-52. On overbreadth, the defendants state medac only made a 50 mg/ml formulation in a water based solvent, and extending the monopoly of Asserted Claims by claiming concentrations, solvents, and treatment indications that were not actually made or disclosed constitutes covetous claiming.

[262] In view of my determination on obviousness, issues of inutility, insufficiency, and overbreadth do not arise for claim $10^{1\text{-}9}$. The defendants arguments are premised on the Court's acceptance that concerns about toxicity or safety would have prevented the skilled person from using a methotrexate solution more concentrated than 25 mg/ml. The defendants' experts' opinions on these invalidity grounds were premised on such assumptions—for example, the experts were asked to assume that a skilled person would be concerned about potential side

effects from subcutaneous administration of 50 mg/ml methotrexate formulation, or that irritancy and injection pain for subcutaneously administered methotrexate was a concern at concentrations greater than 25 mg/ml. The findings made in the context of the obviousness analysis are at odds with these assumptions.

[263] While the defendants also allege that medac did not demonstrate or soundly predict the utility of the claimed formulations for bronchial asthma or Alzheimer's disease, these allegations do not relate to claim $10^{1\text{-}9}$ and it is unnecessary to address them.

## X. **Damages**

[264] In view of my findings, the issue of remedy does not arise. However, since infringement was conceded, and since the disputed points on remedy are narrow and can be resolved independently of my findings on validity, I will address remedies in case of an appeal.

[265] The plaintiffs argue they would be entitled to the following:

i. a declaration of infringement, which should flow automatically from the defendants' concession;

ii. a permanent injunction due to the defendants' at-risk launch and continued infringement; the plaintiffs contend there is no equitable reason to deny them an injunction, and furthermore, an injunction serves the public interest in the enforceability of the patent system (*Eurocopter v Bell Helicopter Textron Canada Limitée*, 2012 FC 113 at para 397);

iii. an order for delivery up or destruction as a standard remedy aligned with an injunction;

iv. damages (the plaintiffs did not elect an accounting of the defendants' profits).

[266] The defendants do not take a position on i to iii, above. I am satisfied that a declaration of infringement, a permanent injunction, and an order for delivery up would be appropriate remedies for infringing a valid Asserted Claim, although I have not considered and I make no comment on the precise scope or language of such relief.

[267] With respect to damages, the only expert evidence was from the plaintiffs' expert Mr. Harington. The defendants did not serve a responding expert report on damages.

[268] The defendants assert that the plaintiffs have not met their burden to establish the assumptions upon which Mr. Harington's expert opinion was based. However, if they are liable for damages, the defendants state Mr. Harington's calculations should be reduced to account for: (i) the plaintiffs' failure to prove their fixed costs; and (ii) Mr. Harington's concession on cross-examination that there was an error in his per-unit transfer price calculation, representing a difference of about $0.90 per unit of lost sales.

[269] With respect to the assumptions, I agree with the plaintiffs that they have established the two assumptions they asked Mr. Harington to make for the purposes of his opinion. The two assumptions were: (i) absent the defendants' market entry, medac's licensees would not have reduced the price of Metoject® products in September 2020; and (ii) had the Accord Products not been available for sale in Canada, the equivalent number of Accord Product units would have been sold by medac's licensees as Metoject® products. The defendants did not lead evidence

challenging either assumption and I find both were established by Mr. Will's testimony and the parties' agreed statement of facts.

[270] As noted above, the two specific errors the defendants raise with Mr. Harington's damages calculation are that the plaintiffs failed to prove their fixed costs and that Mr. Harington made a mistake in his per-unit price transfer calculation.

[271] On the first error, the defendants contend Mr. Harington made an assumption about which costs were categorized as incremental costs and which were categorized as fixed costs. This is important because Mr. Harington only deducted incremental costs from his calculation of the plaintiffs' "but for" lost sales revenues. He did not deduct fixed costs. The defendants say Mr. Harington agreed on cross-examination that the fixed and incremental cost categories did not come from the plaintiffs' documents—he had seen nothing from the plaintiffs confirming which costs were categorized as fixed costs and which were categorized as incremental costs. The defendants contend the plaintiffs were in the best position to lead such evidence. They urge the Court to draw a negative inference from the plaintiffs' failure to do so, and find that all costs should be deducted from the plaintiffs' revenues.

[272] On the second error, the defendants submit Mr. Harington agreed on cross-examination that the per-unit cost to medac's licensee should have been about $0.90 higher. As a result, the damages calculation was inflated by about $0.90 per unit.

[273] I agree with the plaintiffs that Mr. Harington did not rely on an assumption about whether costs were fixed or incremental. Rather, after reviewing documents and the discovery transcripts

related to the plaintiffs' business and finances, Mr. Harington decided based on his expertise how the various costs should be categorized.

[274] The defendants cross-examined Mr. Harington on this point. I agree with the plaintiffs that Mr. Harington testified that he made a determination on how costs should be categorized based on his expertise. While Mr. Harington and defendants' counsel later used the word "assumption", it was not clear that counsel was challenging Mr. Harington's evidence that cost categorization was his opinion. I agree with the plaintiffs that Mr. Harington was likely not alive to any implication from the use of that word, and I am not satisfied that Mr. Harington's cross-examination testimony undermined his opinion on how costs should be categorized.

[275] I also agree with the plaintiffs that there is no basis to draw an adverse inference. The defendants had discovery of the plaintiffs' financial information. They could have adduced evidence to refute Mr. Harington's categorization of fixed and incremental costs and they did not do so.

[276] Turning to the second error, it was clear from Mr. Harington's cross examination that he immediately recognized his mistake—even before counsel finished his question—and readily conceded that the mistake inflated the damages calculations by about $0.90 per unit. Mr. Harington stated he would be able to revise his calculation in accordance with any instructions from the Court, and he would also be able to update his calculation based on financial information from the defendants up to the date of an injunction.

[277] The plaintiffs acknowledge and I agree that Mr. Harington's damages calculations would need to be revised to correct his mistake.

[278] Mr. Harington's calculations were based on information current to March 31, 2022. In my view, had the plaintiffs been successful, they would have been entitled to damages up to the date of an injunction: *Teva Canada Limited v Pfizer Canada Inc*, 2017 FC 332 at para 314-316 [*Teva FC*]; *Varco Canada Limited v Pason Systems Corp*, 2013 FC 750 at para 426. The plaintiffs submit it is appropriate for the Court to remain seized of a matter until final calculations to the date of an injunction are agreed to, or settled by the Court. If the plaintiffs had been successful, I agree with them that it would have been appropriate for the Court to remain seized of the matter pending an agreement or further determination on Mr. Harington's corrected and updated damages calculation: *Teva FC* at paras 5-6, 316.

## XI. **Conclusion**

[279] The plaintiffs' action is dismissed. The defendants have established that the Asserted Claims are obvious and their counterclaim for a declaration of invalidity pursuant to subsection 60(1) of the *Patent Act* is granted.

[280] The parties did not make cost submissions at trial. If the parties reach an agreement on costs and require a cost order from this Court, they shall provide joint written submissions together with a draft order for the Court's consideration within 10 days. If the parties are unable to agree on costs, they shall submit a proposal and schedule for cost submissions within 10 days.

**JUDGMENT in T-1007-20**

**THIS COURT'S JUDGMENT is that**:

1. The action is dismissed.
2. The counterclaim is allowed in part. Claims 1 to 10, 18 to 22, 35, and 39 of Canadian Patent No 2,659,662 titled "Concentrated Methotrexate Solutions" are invalid for obviousness.
3. The Court has not ruled on costs. If the parties reach an agreement on costs and require a cost order from this Court, they shall provide joint written submissions together with a draft order for the Court's consideration within 10 days of this Judgment. If the parties are unable to agree on costs, they shall submit a proposal and schedule for cost submissions within 10 days of this Judgment.

"Christine M. Pallotta"
Judge

## SCHEDULE A

### A. Pleaded Prior Art

1. Alsufyani et al, "The role of subcutaneous administration of methotrexate in children with juvenile idiopathic arthritis who have failed oral methotrexate" (2004) 31:1 J Rheumatology 179 (**Alsufyani 2004)**

2. Arthur, Jubb & Homer, "Self-injection of gold and methotrexate" (2001) 28:1 J Rheumatology 212

3. Arthur, Jubb & Homer, "A study of parenteral use of methotrexate in rheumatic conditions" (2002) 11:2 J Clinical Nursing 256

4. Balis et al, "Pharmacokinetics of subcutaneous methotrexate" (1998) 6:12 J Clinical Oncology 1882 (**Balis 1988**)

5. Black et al, "Methotrexate therapy in psoriatic arthritis; double-blind study on 21 patients" (1964) 7 J American Medical Assoc 743

6. Brooks et al, "Pharmacokinetics of methotrexate administered by intramuscular and subcutaneous injections in patients with rheumatoid arthritis" (1990) 33:1 Arthritis & Rheumatism 91 (**Brooks 1990**)

7. Feagan et al, "Methotrexate for the treatment of Crohn's disease: The North American Crohn's Study Group Investigators" (1995) 332:5 New England J Medicine 292

8. Hoekstra et al, "Bioavailability of higher dose methotrexate comparing oral and subcutaneous administration in patients with rheumatoid arthritis" (2004) 31:4 J Rheumatology 645 (**Hoekstra 2004**)

9. Hoffmeister, “Methotrexate in Rheumatoid Arthritis” (1972) 15:1 Arthritis and Rheumatism 114

10. Hoffmeister, “Methotrexate therapy in rheumatoid arthritis: 15 years experience” (1983) 75:6A American J Medicine 69

11. Hospira UK Ltd, “Methotrexate 100 mg/ml Injection”, Package Insert (November 2005)(**Hospira**)

12. Jansen, Janssen & Nagtegaal, (translation) “Intramuscular and subcutaneous administration in rheumatoid arthritis, Methotrexate outside the clinic” (1999) 134:46 Pharmaceutisch Weekblad 1592 (**Jansen 1999**)

13. Jørgensen et al, “Pain assessment of subcutaneous injections” (1996) 30 Annals Pharmacotherapy 729 (**Jørgensen 1996**)

14. Kurnick et al, “Bioavailability of oral vs. subcutaneous low-dose methotrexate in patients with Crohn’s disease” (2003) 18 Alimentary Pharmacology Therapeutics 57

15. Moitra et al, “Caveats to the use of parenteral methotrexate in the treatment of rheumatic disease” (2005) 44:2 Rheumatology 256

16. *Physicians’ Desk Reference*, 57th ed (New Jersey: Thomson PDR, 2003) 3415 (entry for methotrexate)

17. Russo & Katsicas, “Tolerance of parenteral, higher dose methotrexate in children with juvenile chronic arthritis” (2000) 18:3 Clinical Experimental Rheumatology 425 (**Russo 2000**)

18. US Patent No. 6544504 “Combined use of interleukin 10 and methotrexate for immunomodulatory therapy” (8 April 2003) (**US 504**)

19. Weinblatt, “Methotrexate” in Kelley et al, *Textbook of Rheumatology*, 4th ed (Philadelphia: WB Saunders Company, 1993) 767

20. Wright & Newton, “Stability of methotrexate injection in prefilled, plastic disposable syringes” (1998) 45:3 Intl J Pharmaceutics 237 (**Wright 1988**)

21. Wyeth Pharmaceuticals, “Methotrexate Sodium for Injection” (2004) (**Wyeth**): A data sheet that provides information on a methotrexate product sold as a powder for reconstitution with an appropriate sterile, preservative-free medium.

22. Zackheim, “Subcutaneous administration of methotrexate” (1992) 26:6 J American Academy Dermatology 1008

**B. <u>Additional References</u>**

1. American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines, “Guidelines for the Management of Rheumatoid Arthritis: 2002 Update” (2002) 46:2 Arthritis & Rheumatism 328

2. Aulton & Taylor, *Aulton’s Pharmaceutics: The Design and Manufacture of Medicines*, 4th ed (London: Churchill Livingstone Elsevier, 2013) (**Aulton’s**)

3. Bernstein, Bernstein & Bernstein, “How does auranofin compare with methotrexate and cyclosporin as a corticosteroid-sparing agent in severe asthma?” (1997) 8:3 BioDrugs 205

4. Borchers et al, “The use of methotrexate in rheumatoid arthritis” (2004) 34:1 Seminars in Arthritis & Rheumatism 465

5. Boylan & Nail, “Parenteral Products” in Banker & Rhodes, eds, *Modern Pharmaceutics*, 4th ed (New York: Marcel Dekker, Inc, 2002) chapter 12

6. Busse et al, “Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma–Summary Report 2007” (2007) 120:5 J Allergy & Clinical Immunology Supplement S94

7. Chabner et al, “Chemotherapy of Neoplastic Diseases” in Brunton, Lazo & Parker, eds, *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 11th ed (New York: McGraw Hill, 2005) 1315 (**Goodman and Gilman’s**)

8. Corrigan et al, “Methotrexate therapy of oral corticosteroid-dependent asthmatics reduces serum immunoglobulins: Correlation with clinical response to therapy” (2005) 35:5 Clinical & Experimental Allergy 579

9. Cronstein, “Low-dose methotrexate: A mainstay in the treatment of rheumatoid arthritis” (2005) 57:2 Pharmacological Reviews 163

10. Farber, “Some observations on the effect of folic acid antagonists on acute leukemia and other forms of incurable cancer” (1949) 4:2 Blood 160

11. Feber & Krasnicanova, “Measures of Body Surface Area in Children” in Preedy, ed, *Handbook of Anthropometry* (New York: Springer, 2012) 1249

12. Firestein et al, *Kelley's Textbook of Rheumatology*, 8th ed (Philadelphia: Saunders, 2009)

13. Formulary Search, “Limited Use Note(s): Adalimumab” (last accessed 3 May 2022), online: *Government of Ontario* <formulary.health.gov.on.ca>

14. Held-Warmkessel, “Methotrexate” (2000) 4:4 Clinical J Oncology Nursing 187

15. Kaldan, “Expanding role of biologic agents in rheumatoid arthritis” (2002) 66 J Rheumatology Supplement 27

16. Kallstrom, “Evidence-based asthma management” (2004) 49:7 Respiratory Care 783

17. Karch, “Lippincott’s Nursing Drug Guide”, 2007 (entry on methotrexate)

18. Kerrigan & McInnes, “Reflections on ‘older’ drugs: learning new lessons in rheumatology” (2020) 16:3 Nature Reviews Rheumatology 179

19. Klareskog et al, “Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial” (2004) 363 Lancet 675

20. Kozminski et al, “Overview of Dual-Acting Drug Methotrexate in Different Neurological Diseases, Autoimmune Pathologies and Cancers” (2020) 21:10 Intl J Molecular Sciences 3438

21. McGeer et al, “Anti-inflammatory drugs and Alzheimer disease” (1990) 335 Lancet 1037

22. McGeer, Rogers & McGeer, “Inflammation, anti-inflammatory agents and Alzheimer disease: The last 12 years” (2006) 9:3 J Alzheimers Disease Supplement 271

23. Mosteller, “Simplified calculation of body-surface area” (1987) 317:17 New England J Medicine 1098

24. Niehues et al, “Evidence-based use of methotrexate in children with rheumatic diseases: a consensus statement of the Working Groups Pediatric Rheumatology Germany (AGKJR) and Pediatric Rheumatology Austria” (2005) 25 Rheumatology Intl 169

25. Oberholzer, Oberholzer & Moldawer, “Interleukin-10: A complex role in the pathogenesis of sepsis syndromes and its potential as an anti-inflammatory drug” (2002) 30:1 Critical Care Medicine Supplement S58

26. Pavy et al, “Methotrexate therapy for rheumatoid arthritis: clinical practice guidelines based on published evidence and expert opinion” (2006) 73 Joint Bone Spine 388

27. Petty et al, “Revision of the proposed classification criteria for juvenile idiopathic arthritis: Durban, 1997” (1998) 25:10 J Rheumatology 1991

28. Rady Children’s Specialists, Division of Allergy, Immunology & Rheumatology, “What’s in a Name? Names and Types of Childhood Arthritis”

29. Rojanasakul & Malanga, “Parenteral Routes of Delivery” in Ghosh & Jasti, eds, *Theory and Practice of Contemporary Pharmaceutics* (Boca Raton: CRC Press, 2004) chapter 13 (**Contemporary Pharmaceutics**)

30. Rue, Waterhouse & Cocchetto, “Volmax: simulated gastrointestinal pH and agitation studies” (1991) 25:4 DICP 438

31. Sinko, “Drug Delivery Systems” in Troy, ed, *Martin’s Physical Pharmacy and Pharmaceutical Sciences*, 5th ed (Baltimore: Lippincott Williams & Wilkins) 629

32. St. Clair et al, “Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial” (2004) 50:11 Arthritis & Rheumatism 3432

33. Teva Pharmaceuticals Ltd, “Abitrexate”, Package Insert, 2000

34. Tian & Cronstein, “Understanding the mechanisms of action of methotrexate: implications for the treatment of rheumatoid arthritis” (2007) 65:3 Bulletin NYU Hospital for Joint Diseases 168

35. United States Pharmacopeia, *USP 29* (Maryland: United States Pharmacopeial Convention, 2006) (**USP**)

36. Usach et al, “Subcutaneous Injection of Drugs: Literature Review of Factors Influencing Pain Sensation at the Injection Site” (2019) 36:11 Advances in Therapy 2986

37. Verbraecken et al, “Body surface area in normal-weight, overweight, and obese adults: a comparison study” (2006) 55:4 Metabolism - Clinical & Experimental 515

38. Weinblatt et al, “A trial of etanercept, a recombinant tumor necrosis factor receptor: Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate” (1999) 340:4 New England J Medicine 253

39. Weinblatt, “Rheumatoid arthritis: More aggressive approach improves outlook” (2004) 71:5 Cleveland Clinic J Medicine 409

**FEDERAL COURT**

**SOLICITORS OF RECORD**

| | |
|---|---|
| **DOCKET:** | T-1007-20 |
| **STYLE OF CAUSE:** | MEDEXUS PHARMACEUTICALS INC., MEDEXUS INC. and MEDAC GESELLSCHAFT FÜR KLINISCHE SPEZIALPRÄPARATE MBH v ACCORD HEALTHCARE INC. AND INTAS PHARMACEUTICALS LTD. |
| **PLACE OF HEARING:** | TORONTO, ONTARIO |
| **DATE OF HEARING:** | JANUARY 9-13, 2023, JANUARY 16-18, 2023 and JANUARY 30, 2023 |
| **JUDGMENT AND REASONS**: | PALLOTTA J. |
| **CONFIDENTIAL JUDGMENT AND REASONS ISSUED:** | MARCH 14, 2024 |
| **PUBLIC JUDGMENT AND REASONS ISSUED:** | MARCH 26, 2024 |

**APPEARANCES:**

| | |
|---|---|
| Melanie Baird<br>Andrew Skodyn<br>Sean Jackson<br>Dylan Churchill | FOR THE PLAINTIFFS/<br>DEFENDANTS BY COUNTERCLAIM |
| Nisha Anand<br>Kevin Siu<br>Justin Kearsley-Ho | FOR THE DEFENDANTS/<br>PLAINTIFFS BY COUNTERCLAIM |

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| Gilbert's LLP<br>Barristers and Solicitors<br>Toronto, Ontario | FOR THE DEFENDANTS/<br>PLAINTIFFS BY COUNTERCLAIM |