UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

FRONTIER THERAPEUTICS, LLC

Petitioner

v.

MEDAC GESELLSCHAFT FÜR KLINISCHE SPEZIALPRÄPARATE MBH

Patent Owner

Inter Partes Review Case No. Unassigned
Patent No. 8,664,231
Title: Concentrated Methotrexate Solutions

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 8,664,231

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I. INTRODUCTION

Frontier Therapeutics, LLC ("Petitioner") files this Petition for *Inter Partes* Review ("Petition") seeking cancellation of claims 1-22 ("challenged claims") of U.S. Pat. No. 8,664,231 to Will, titled "Concentrated Methotrexate Solutions" ("the '231 Patent") (Ex. 1001).

II. OVERVIEW

This Petition advances five grounds of invalidity against claims 1-22 of the '231 Patent, including the same grounds that were previously instituted by the Patent Trial and Appeal Board ("the Board") in an earlier-filed *inter partes* review. *See* '091 IPR Institution (Ex. 1033). With particular regard to those grounds, the Petitioner asserts that the challenged claims of the '231 Patent are: anticipated under 35 U.S.C. § 102(b) by Grint (Ex. 1003), and/or are obvious under 35 U.S.C. § 103(a) over one or more of 1) Grint; 2) Insulin Admin. (Ex. 1015); 3) Alsufyani (Ex. 1006); 4) PDR (Ex. 1007); 5) Hospira (Ex. 1009); and 6) Brooks (Ex. 1008).

Each of the limitations of the challenged claims of the '231 Patent is taught by the prior art. First, as explained by the Board in the '091 IPR Institution with respect to claims 1, 2, 4-6, 11-13, 17, and 22, "Grint discloses a method for treating inflammatory autoimmune diseases in a patient, including rheumatoid arthritis, comprising administering a medication comprising methotrexate in a pharmaceutically acceptable solvent." P. 8. The Board also noted that "Grint

discloses a treatment method that involves administering methotrexate parenterally, including subcutaneously, from a unit dosage form containing methotrexate at a concentration of more than 30 mg/ml, i.e., 0.1 to about 40 mg/ml of carrier." *Id*. at 8-9. This, according to the Board, "reasonably establishes that Grint correlates treatment of a specific disease with a specific route of administration (subcutaneous) and use of a specific concentration range of a methotrexate solution." *Id*. at 9.

The Board was not persuaded by the Patent Owner's contention that a skilled artisan would not look to the "lower end of the dosage and concentration" disclosed in Grint. According to the Board, the Patent Owner failed to provide any evidence demonstrating that "a skilled artisan would have understood that only the lower end of Grint's disclosed concentration range for a parenteral unit dosage form would have applied to a subcutaneous injection." *Id*. at 10. More simply, however, the Board recognized this argument as being a red herring because "the claims at issue do not recite administering any specific dosages ranges." *Id*.

With regard to claims 7-10, 14-16, and 19-21, the Board concluded there was a "reasonable likelihood" that those claims were obvious over Grint and Insulin Admin. *Id*. at 13. While Grint "does not expressly disclose that its methotrexate is packaged in a form suitable for self-administration," Insulin

Admin. discloses "the use of a 'pen-like device,' i.e., an injection device or a pen injector, and the use of a 'prefilled syringe,' i.e., a 'ready-made syringe' for self-administration of insulin." *Id*. at 12 (citation omitted). Though it was acknowledged that Insulin Admin. does not specifically teach an injection device comprising methotrexate, this alone was not deemed significant given "the '231 Patent acknowledges that ready-made syringes containing methotrexate were also known in the prior art." *Id*. at 13.

The Board similarly held that the additional limitations provided by dependent claim 18 are likely obvious over Grint and Alsufyani, at least because "one of ordinary skill in the art would have been motivated, with a reasonable expectation of success, to use highly concentrated solutions of methotrexate to treat juvenile rheumatoid arthritis, based on the combined teachings of Grint and Alsufyani." *Id*. at 15.

The Board further held that claims 1-5, 11-13, 17, and 22 are likely obvious over the PDR or Hospira in view of Brooks. *Id*. at 22. With particular regard to claim 3, the Board found that the "PDR and Hospira each teach a method for treating psoriasis, an inflammatory autoimmune disease, comprising administering methotrexate in a pharmaceutically acceptable solvent at a concentration of more than 50 mg/ml." *Id*. at 20. Though the Board conceded that "the PDR and Hospira

each teach administering the methotrexate injection intramuscularly, Petitioner has shown sufficiently at this stage in the proceeding that a person of ordinary skill in the art would have had a reason to administer the injections disclosed by the PDR and Hospira subcutaneously based upon the teachings of Brooks." *Id*. at 21. For similar reasons, the Board concluded that claims 7-10, 14-16, and 19-21 are likely obvious over the PDR or Hospira in view of Brooks and Insulin Admin. *Id*. at 22-23.

In light of the foregoing positions taken by the Board, the Petitioner advances Grounds 1-5 below, which detail the lack of novelty and nonobviousness of the challenged claims. *See infra*, § XII.

Moreover, the Patent Owner cannot demonstrate secondary indicia of nonobviousness of claims 1-22. At no time during the proceedings of the '091 IPR did Patent Owner attempt to argue secondary indicia of nonobviousness in an effort to overcome Petitioner's strong case of *prima facie* obviousness. Unsurprisingly, the Patent Owner consciously neglected to reiterate the secondary consideration positions it previously advanced during the prosecution of the '231 Patent, which were contradictory and ultimately meritless. *See infra*, § XIII.

For at least these reasons and those discussed below in further detail, Petitioner has a reasonable likelihood of prevailing on the assertion that the

challenged claims are anticipated and/or obvious in view of the prior art references discussed herein.

III. GROUNDS FOR STANDING - § 42.104(a)

Petitioner certifies pursuant to 37 C.F.R. § 42.104(a) that the patent for which review is sought is available for *inter partes* review and that the Petitioner is not barred or estopped from requesting an *inter partes* review challenging the patent claims on the grounds identified in this Petition.

IV. MANDATORY NOTICES UNDER 37 C.F.R. § 42.8

A. Real Party in Interest

In accordance with 37 C.F.R. § 42.8(b)(1), the Petitioner, Frontier Therapeutics, LLC, is identified as the real party-in-interest. No person or entity other than Frontier Therapeutics, LLC has authority to direct or control (i) the timing of, filing of, content of, or any decisions or other activities relating to this Petition or (ii) any timing, future filings, content of, or any decisions or other activities relating to the future proceedings related to this Petition.

B. Related Matters

In accordance with 37 C.F.R. § 42.8(b)(2), Petitioner identifies the following matters: Judicial Matters: *Medac Pharma, Inc. et al. v. Antares Pharma Inc. et al*., NJD-1-14-cv-01498 (D.N.J.). Administrative matters: pending U.S. Patent Appl.

No. 14/635,542; *Petition for Inter Partes Review by Antares Pharma Inc. et al.*, PTAB-IPR2014-01091.

C. Lead and Backup Counsel

In accordance with 37 C.F.R. § 42.8(b)(3), Petitioner identifies counsel:

Lead Counsel	**Back-Up Counsel**
Dr. Gregory Gonsalves Reg. No. 43,639 2216 Beacon Lane Falls Church, VA 22043 (571) 419-7252 gonsalves@gonsalveslawfirm.com	Christopher Casieri McNeely, Hare & War LLP 12 Roszel Road, Suite C104 Princeton, NJ 08540 Phone: 609 731 3668 chris@miplaw.com

V. SERVICE INFORMATION

Pursuant to 37 C.F.R. § 42.8(b)(4), Petitioner consents to electronic service provided to the email addresses provided immediately above.

VI. PAYMENT OF FEES UNDER §§ 42.15(a) AND 42.103

The required fees are submitted herewith.

VII. STATEMENT OF THE PRECISE RELIEF REQUESTED AND THE REASONS THEREFOR (37 C.F.R. § 42.22(a))

Petitioner requests IPR and cancellation of claims 1-22 of the '231 Patent based on one or more of the grounds under pre-AIA 35 U.S.C. § 102(b) and 35 U.S.C. § 103(a) set forth herein. Petitioner's detailed statement of the reasons for the relief requested is set forth in § XII below.

VIII. THE '231 PATENT

A. The Specification

The '231 Patent is a §371 National Stage Entry of PCT Application No. PCT/EP2007/006491, filed July 20, 2007, which claims the benefit of German Application No. DE 10 2006 033 837, filed July 21, 2006. Ex. 1001 at Front Cover. The '231 Patent is titled "Concentrated Methotrexate Solutions," and it describes and claims a method of treating inflammatory autoimmune diseases with "concentrated" methotrexate (MTX), wherein the MTX is administered subcutaneously (*i.e.*, under the skin). The '231 Patent's specification acknowledges that methods of treating inflammatory autoimmune diseases with MTX were known in the art at the time of filing, as was the subcutaneous route of administration. *Id*. at 2:34-36; 2:41-42. Thus, the only alleged improvement in the '231 Patent is the use of "concentrated" MTX solutions ("more than 30 mg/ml" are claimed) in performing the methods disclosed in the prior art. *Id*. at 1:1-10; *see also* Ex. 1002 at 20, 3/21/2012 Office Action ("OA") Response. Although each claim of the '231 Patent is directed to a method of treating a patient having an inflammatory autoimmune disease with "concentrated" MTX, the '231 Patent does not include a single working example showing administration of any concentration of MTX to a patient.

B. The Claims

Claim 1, the only independent claim in the ’231 Patent, recites a method for treating inflammatory autoimmune diseases in a patient in need thereof, comprising subcutaneously administering to said patient a medicament comprising methotrexate in a pharmaceutically acceptable solvent at a concentration of more than 30 mg/ml. Ex. 1001 at 8:43-47.

Claim 2 depends from claim 1, and recites that the MTX is present at a concentration of more than 30 mg/ml to 100 mg/ml. *Id*. at 8:48-50.

Claim 3 depends from claim 2, and recites that the MTX is present at a concentration of about 50 mg/ml. *Id*. at 8:50-52.

Claim 4 depends from claim 1, and recites that the pharmaceutically acceptable solvent is selected from water, water for injection purposes, water comprising isotonization additives and sodium chloride solution. *Id*. at 8:53-56.

Claim 5 depends from claim 1, and recites that 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. *Id*. at 8:57-62.

Claim 6 depends from claim 5, and recites that the inflammatory autoimmune disease is rheumatoid arthritis. *Id*. at 8:63-64.

Claim 7 depends from claim 1, and recites that the medicament is present in a form suitable for patient self-administration. *Id*. at 8:65-67.

Claim 8 depends from claim 1, and recites that the medicament is contained in an injection device for a single application. *Id*. at 9:1-3.

Claim 9 depends from claim 8, and recites that the injection device contains a dosage of 5 to 40 mg of methotrexate. *Id*. at 9:4-5.

Claim 10 depends from claim 8 or claim 9, and recites that the injection device is a ready-made syringe. *Id*. at 9:6-7.

Claim 11 depends from claim 1, and recites that the medicament is contained in a storage container. *Id*. at 9:8-9.

Claim 12 depends from claim 11, and recites that the storage container contains a total dosage amount of 5 to 5,000 mg. *Id*. at 9:10-11.

Claim 13 depends from claim 11, and recites that the storage container is an injection bottle, a vial, a bag, a glass ampoule, or a carpule. *Id*. at 9:12-14.

Claim 14 depends from claim 13, and recites that the storage container is a carpule and wherein said carpule is suitable for administering the medicament by means of an injection device. *Id*. at 9:15-18.

Claim 15 depends from claim 14, and recites that the carpule and the pen injector are provided such that multiple applications of single dosages can be

administered. *Id*. at 9:19-21.

Claim 16 depends from claim 15, and recites that the single dosages per application can be adjusted to 5 to 40 mg each of methotrexate. *Id*. at 10:1-3.

Claim 17 depends from claim 4, and recites that the sodium chloride solution is isotonic sodium chloride solution. *Id*. at 10:4-5.

Claim 18 depends from claim 6, and recites that the rheumatoid arthritis is juvenile rheumatoid arthritis. *Id*. at 10:6-7.

Claim 19 depends from claim 9, and recites that the injection device contains a dosage selected from 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. *Id*. at 10:8-11.

Claim 20 depends from claim 14, and recites that the injection device is a pen injector. *Id*. at 10:12-13.

Claim 21 depends from claim 16, and recites that the single dosages of methotrexate per application is adjusted to be 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. *Id*. at 14-17.

Claim 22 depends from claim 1, and recites that the methotrexate is present at a concentration of from 40 mg/ml to 80 mg/ml. *Id*. at 18-20.

C. The Prosecution History

The application that led to the ’231 Patent was rejected in a first, non-final OA dated December 21, 2011. Ex. 1002 at 2-12, 12/21/11 OA. At the time of this

OA, claims 1-11 and 13-17 were pending. Claim 1, the only independent claim, recited uses of methotrexate at a concentration of more than 30 mg/ml for subcutaneous administration to treat inflammatory autoimmune diseases. *Id*. at 1. The Examiner rejected claims 1-11 and 13-17 as obvious under 35 U.S.C. § 103(a) over Hoekstra (Ex. 1004) in view of various secondary references. *Id*. at 6-10. The Examiner alleged that Hoekstra taught methods for administering MTX to patients via the subcutaneous route, wherein the total dosage (in mg) of MTX was greater than 25 mg per week. *Id*. The Examiner recognized that Hoekstra did not teach the claimed "more than 30 mg/ml" concentrations of MTX, but concluded that the claims were nevertheless obvious because "the determination of the optimum characterization of the composition and dosage amounts would have been a matter well within the purview of one of ordinary skill in the art, at the time of invention, through no more than routine experimentation." *Id*.

Applicant responded to the obviousness rejection on March 21, 2012, by arguing that Hoekstra "clearly represents the closest prior art" but does not provide any teaching with regard to "the crucial feature of the present invention," that is "the particularly high concentration of the active agent methotrexate in the solution, i.e., more than 30 mg/mL." Ex. 1002 at 20, 3/21/2012 OA Response. Applicant argued, without evidentiary support, that the claimed invention "is not a

mere optimization of ranges or regimens which is obtained by mere routine experimentation" because "methotrexate clearly is an active agent which is also used in cancer therapy, so that a person skilled in the art would have been very cautious to increase the concentration of the active agent in a subcutaneously administered solution." *Id*. at 9. Applicant argued further, again without evidentiary support, that "it was not at all obvious at the time of the present invention that toxicity and bioavailability of methotrexate solutions with higher concentrations would be acceptable." *Id*. Although Applicant admitted that highly concentrated forms of MTX were "on the market" as of the priority date of the invention, it erroneously asserted that they were "solely marketed and approved for treatment of cancer. …" *Id*. at 10.

Additionally, in an attempt to rebut the Examiner's *prima facie* case of obviousness, Applicant submitted a copy of a 2010 scientific article by Müller-Ladner (Ex. 1011), and argued that the article provided evidence of unexpected results. Ex.1002 at 21, 3/21/2012 OA Response. Applicant alleged that Müller-Ladner described a comparison between a 50 mg/ml solution of MTX (high-concentration formulation; "HC") and a 10 mg/ml solution of MTX (medium-concentration formulation, "MC"), and concluded that subcutaneous injection of the 50 mg/ml MTX solution in patients with RA was better tolerated than the

subcutaneous injection of the 10 mg/ml MTX solution. *Id*. Despite the fact that Applicant had previously acknowledged that the Hoekstra reference, disclosing a 25 mg/ml concentration of MTX for subcutaneous administration, was the closest prior art, Applicant nevertheless concluded that the "improvement" seen with the higher concentrated 50 mg/ml MTX solution of Müller-Ladner was a "surprising technical effect which was unexpectedly observed" when compared to the higher volume, but less concentrated 10 mg/ml MTX solution. *Id*.

In this same March 21, 2012 response, Applicant argued that Zackheim (Ex. 1010), cited by the Examiner in the § 103 rejection, taught away from the invention because when administering a dose of MTX greater than 50 mg, the authors "chose" to maintain the concentration of MTX at 25 mg/ml and to use two injection sites with 25 mg/ml at each site, rather than to increase the concentration of the methotrexate solution to 50 mg/ml, for example, and administer only a single injection. *Id*. at 10.

A telephone interview was conducted between Applicant's representative and the Examiner on December 23, 2013, where "[a]llowable subject matter was discussed. …" Ex. 1002 at 25, 12/23/13 Examiner Interview. A Notice of Allowance was issued on January 7, 2014. *Id*. at 1. The Examiner stated in the Reasons for Allowance that Applicant's arguments submitted on March 21, 2012,

were persuasive, and that "the limitation 'at a concentration of more than 30 mg/ml' is novel and not in a range that would have been found obvious through optimization." *Id*. at 3. Presumably based on Applicant's misrepresentation that highly concentrated forms of MTX were "solely marketed and approved for treatment of cancer," (*see* OA Response at 10), the Examiner determined that "Applicant is correct in stating that this concentration would have been avoided and above the maximum range in the art." *Id*.

IX. LEVEL OF ORDINARY SKILL IN THE ART

The level of skill in the art is apparent from the cited art. Further, a person having ordinary skill in the art would have either a Pharm. D. or a Ph.D. in pharmacy, pharmacology, or a related discipline; an M.D. or D.O. with experience in using MTX; or a BS in pharmacy with at least two years of experience formulating active pharmaceutical ingredients for injection. A person of ordinary skill in the art would collaborate with others having expertise in, for example, methods of treating disease and administering medicines. Gershwin Decl. (Ex. 1012) at ¶ 39; Gammon Decl. (Ex.1013) at ¶ 16.

X. CLAIM CONSTRUCTION

In an *inter partes* review, "[a] claim in an unexpired patent shall be given its broadest reasonable construction in light of the specification of the patent in which

it appears." 37 C.F.R. § 42.100(b). Thus, the words of a claim are given their plain meaning unless that meaning is inconsistent with the specification. *In re Zletz*, 893 F.2d 319, 321 (Fed. Cir. 1989).

A. "Subcutaneously"

The term "subcutaneously" means "under the skin." Gershwin Decl. (Ex. 1012) at ¶ 49; Ex. 1001 at 5:1-5.

B. "Pharmaceutically acceptable solvent"

The term "pharmaceutically acceptable solvent" means "a solvent that is safe for administration to patients, including humans, that will not interfere with the active pharmaceutical substance or other component in the solution." Gammon Decl. (Ex. 1013) at ¶ 21; Ex. 1001 at 3:28-36.

C. "Injection device"

The term "injection device" means "a device that permits a medicament to be injected into a patient." Gammon Decl. (Ex. 1013) at ¶ 25; Ex. 1001 at 4:19-39.

D. "Ready-made syringe"

The term "ready-made syringe" means "a device containing a medicament that permits the medicament to be injected into a patient." Gammon Decl. (Ex. 1013) at ¶ 29; Ex 1001 at 4:55-59, 5:28-41.

E. "Pen Injector"

The term "pen injector" means "a device that injects a dose of medicament into a patient via a powered or manually inserted hypodermic needle, wherein the device may be for single use or multiple uses, and may be disposable or reusable." Gammon Decl. (Ex. 1013) at ¶ 33; Ex. 1001 at 6:55-7:27.

XI. RELIEF REQUESTED

A. Claims for Which Review is Requested

Petitioner requests IPR under 35 U.S.C. § 311 of claims 1-22 of the '231 Patent, and such cancellation of these twenty-two claims as unpatentable.

B. Statutory Grounds of Challenge

Claims 1-22 are unpatentable under pre-AIA 35 U.S.C. §§ 102 and/or 103 for the following reasons:

Ground	35 USC	Claims	Index of Reference(s)
1	§ 102(b)	1, 2, 4-6, 11-13, 17, and 22	U.S. Patent No. 6,544,504 (Grint) (Ex. 1003)
2	§ 103(a)	7-10, 14-16, and 19-21	Grint and Insulin Admin. (Ex. 1015)
3	§ 103(a)	18	Grint and Alsufyani (Ex. 1006)
4	§ 103(a)	1-5, 11, 12, 13, 17,	PDR (Ex. 1007) or Hospira (Ex.

		and 22	1009) and Brooks (Ex. 1008)
5	§ 103(a)	7-10, 14-16, and 19-21	PDR or Hospira and Brooks, and Insulin Admin.

C. Overview of the Prior Art

MTX has been used since at least the 1950's for the treatment of inflammatory autoimmune diseases such as rheumatoid arthritis (RA) and psoriasis. Ex. 1001 at 1:28-32; Ex. 1014 at S179-80. MTX was approved by the FDA in 1988 as a weekly therapy for treating rheumatoid arthritis. Weinblatt 1993 (Ex. 1018) at 767. Subsequent long-term, controlled trials established that MTX remained effective for treating RA over many years of therapy with acceptable toxicity levels. Ex. 1014 at S180-181, "Long-term safety of methotrexate." MTX has also been shown to be effective in treating chronically active Crohn's disease, another inflammatory autoimmune disease. Gershwin Decl. (Ex. 1012) at ¶ 31.

Methods for treating inflammatory autoimmune diseases via subcutaneous injections of MTX at concentrations up to 40 mg/ml were described before the July 21, 2006, the earliest possible priority date of the '231 Patent. *See* U.S. Patent 5,644,504 ("Grint"; Ex. 1003); *see also* Gershwin Decl. (Ex. 1012) at ¶¶ 56-60. And because it was routine in the art as of 2006 to formulate injectable drugs into ready-made syringes and prior art injection devices such as pen-injectors to

increase patient compliance and comfort, there was nothing inventive about placing the concentrated MTX formulations of Grint into these devices. *See, e.g.*, Ex. 1001 at 6:60-67; Gammon Decl. (Ex. 1013) at ¶¶ 40-42 and 49-54.

Additional art also shows that there was nothing inventive about the methods recited in the '231 Patent claims. For example, Hoekstra teaches methods for treating inflammatory autoimmune diseases via subcutaneous injection of MTX, where the MTX is present at a concentration of 25 mg/ml. Ex. 1004 at 645. Hoekstra does not teach MTX concentrations of "more than 30 mg/ml" as recited in the '231 Patent's claims, but Hoekstra does teach single doses of MTX greater than 25 mg, including 40 mg. The skilled artisan would have been motivated to increase the concentration of Hoekstra's MTX solution to reduce the injectable volume of such doses because Jørgensen (Ex. 1005) teaches that subcutaneously injected solutions should be less than 1 ml to reduce pain and increase patient compliance. *Id*. at 729. This teaching would motivate the skilled artisan to formulate the 40 mg MTX dose of Hoekstra as a solution of less than 1 ml (*i.e.*, a concentration of at least 40 mg/ml). The skilled artisan also would have expected success when administering MTX concentrations greater than 30 mg/ml because MTX solutions having concentrations of up to 125 mg/ml were available in the prior art for intramuscular injection in the treatment of psoriasis. *See, e.g.*, Ex.

1007 ("the PDR"); *see also* Ex. 1009 ("Hospira"); *see also* Gammon Decl. (Ex. 1013) at ¶¶ 39, 57, and 59.

In addition, these prior art concentrated MTX solutions are themselves a basis for unpatentability of the challenged claims. Both the PDR (Ex. 1007) and Hospira (Ex. 1009) teaches methods for treating psoriasis, an inflammatory autoimmune disease, with MTX solutions having concentrations within the claimed ranges, albeit via intramuscular, rather than subcutaneous, routes of administration. Ex. 1007 at 764, middle col.; Ex. 1009 at §§ 4.1, 4.2. Skilled artisans, however, would have been motivated – with a reasonable expectation of success – to administer the MTX solutions disclosed in the PDR and Hospira via subcutaneous routes to patients with inflammatory autoimmune diseases because Brooks (Ex. 1008) discloses that (i) intramuscular and subcutaneous administrations of MTX are "interchangeable," and (ii) subcutaneous administration "may be a more convenient and less painful way of administering low-dose MTX." Ex. 1008 at 91.

XII. DETAILED EXPLANATION OF THE CHALLENGE

A. Ground 1: U.S. Patent No. 6,544,504 (Grint, Ex. 1003) anticipates claims 1, 2, 4-6, 11-13, 17, and 22 under pre-AIA 35 U.S.C. § 102(b)

Methods for treating inflammatory autoimmune diseases via subcutaneous injections of MTX at concentrations greater than 30 mg/ml were known before

July 21, 2006, the earliest possible priority date of the '231 Patent, as evidenced by U.S. Patent 6,544,504 ("Grint," Ex. 1003). Grint issued on April 8, 2003, and is prior art under pre-AIA 35 U.S.C. §102(b). Grint was not considered by the United States Patent and Trademark Office ("USPTO") during prosecution of the '231 Patent.

Grint describes methods for treating autoimmune diseases, including RA and psoriasis, using interleukin 10 (IL-10) and MTX. *See, e.g.*, Ex. 1003 at Abstract. Grint discloses that IL-10 and MTX "may be administered together in a single pharmaceutical composition or separately." *Id*. at 3:21-22. Gershwin Decl. (Ex. 1012) at ¶ 54. Grint also discloses that MTX may be administered "parenterally," and in the examples provided in the patent, some of the patients received MTX subcutaneously, further indicating that the solutions were made with solvents that were safe to administer to patients and did not interfere with the other components of the solution. Ex. 1003 at 5:64-66; 7:54-57; Gershwin Decl. (Ex. 1012) at ¶ 54.

Grint teaches that it is advantageous to formulate parenteral MTX compositions "in unit form for case [sic, ease] of administration and uniformity in dosage." *Id*. at 6:52-54. From this disclosure, a skilled artisan would understand that the MTX composition would be stored in a container, which could include an injection bottle, vial, bag, glass ampule, or carpule. Gammon Decl. (Ex. 1013) at ¶

45. Grint discloses unit doses of MTX in amounts from about 0.1 to 400 mg, most preferably 10 to 25 mg, and that "methotrexate is generally present in from about 0.1 to about 40 mg/ml of carrier." Ex. 1003 at 6:63-7:1. To one of ordinary skill in the art, Grint teaches the subject matter claimed in the '231 Patent—subcutaneous administration of an MTX at concentrations greater than 30 mg/ml to treat inflammatory autoimmune diseases such as RA and psoriasis. Gershwin Decl. (Ex. 1012) at ¶¶ 53-66; Gammon Decl. (Ex. 1013) at ¶¶ 43-47.

To anticipate a claim, a prior art reference must disclose every limitation of the claimed invention, either explicitly or inherently. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987). Moreover, "if granting patent protection on the disputed claim would allow the patentee to exclude the public from practicing the prior art, then that claim is anticipated, regardless of whether [the claim] also covers subject matter not in the prior art." *Atlas Powder Co. v. IRECO, Inc*., 190 F.3d 1342, 1349 (Fed. Cir. 1999), *citing Titanium Metals Corp. v. Banner*, 778 F.2d 775, 781 (Fed. Cir. 1985). Because maintaining patent protection to claims 1, 2, 4-6, 11-13, 17, and 22 of the '231 Patent would exclude the public from practicing Grint, these claims should be canceled.

Even though claims 1, 2, 4-6, 11-13, 17, and 22 of the '231 Patent read on Grint's disclosed methods, Patent Owner may attempt argue that Grint's disclosed

range of MTX concentrations ("0.1 to 40 mg/ml") does not anticipate Patent Owner's claimed ranges of MTX concentrations (e.g., "30 mg/ml to 100 mg/ml" in claim 2, and "40 mg/ml to 80 mg/ml" in claim 22). However, the Federal Circuit has addressed anticipation when a patent claims a range that overlaps with a range disclosed in the prior art.[1] In *Atofina v. Great Lakes Chem. Corp*., 441 F.3d 991 (Fed. Cir. 2006), under facts very different than this case, the Federal Circuit held that the prior art did not anticipate the claimed range. And in *ClearValue, Inc. v. Pearl River Polymers, Inc*., 668 F.3d 1340 (Fed. Cir. 2012), with facts more similar to this case, the Federal Circuit explained and distinguished *Atofina* and held that the prior art range ("150 ppm or less") anticipated the claimed range ("less than or equal to 50 ppm").

ClearValue explained that the claims in *Atofina* recited a "critical" temperature range, and cited evidence in *Atofina* showing that one of ordinary skill would have expected the claimed process to operate differently outside of the claimed temperature range. *See* 668 F.3d at 1345. In *ClearValue*, however, there

[1] In earlier cases, the Federal Circuit has held that prior art ranges anticipated claimed ranges without questioning whether overlapping ranges presented a case of anticipation. *See Atlas Powder Co. v. Ireco Inc*., 190 F.3d 1342, at 1346 (Fed. Cir. 1999).

was "no allegation of criticality [of the claimed range] or any evidence demonstrating any difference across the prior art range." *Id*. Moreover, evidence in *ClearValue* suggested that one skilled in the art would have understood the prior art as teaching values within the ranges claimed in the patent. *Id*.

In the case of the '231 Patent, there is no evidence of criticality of the overlapping range (30-40 mg/ml) or any evidence demonstrating any difference across the prior art range (0.1-40 mg/ml) and the range of the '231 Patent claims. Gershwin Decl. (Ex. 1012) at ¶ 61. To the contrary, the '231 Patent acknowledges that MTX concentrations outside of the claimed range, specifically 10.0 mg/ml, can be administered subcutaneously for the treatment of RA. Ex. 1001 at 4:59-5:11. Moreover, one skilled in the art would have understood Grint as teaching MTX concentrations within the ranges claimed by the '231 Patent. *See* Gershwin Decl. (Ex. 1012) at ¶¶ 58-61, 66. Consequently, similar to *ClearValue*, the MTX concentration range disclosed in Grint, 0.1-40 mg/ml, anticipates the ranges claimed in the '231 Patent, *e.g*. 30-100 mg/ml and 40-80 mg/ml. Thus, Grint teaches each and every limitation of claims 1, 2, 4-6, 11-13, 17, and 22 of the '231 Patent, as shown in detail in the chart below. Accordingly, these claims should be canceled as anticipated by Grint under § 102(b).

1. Ground 1 Claim Chart

Claim	Grint

Claim 1. A method for the treatment of inflammatory autoimmune diseases in a patient in need thereof, comprising	Grint teaches a method for treating inflammatory autoimmune diseases in a patient in need thereof. Ex. 1003 at 2:23-24 ("The present invention provides a method for treating autoimmune disease…."); *see also* Ex. 1003 at 3:4-9 ("The methods of the invention can be used prophylactically or for treatment of established autoimmune disease. Individuals suitable for treatment by the methods of the invention include any individual at risk (predisposed) for developing rheumatoid arthritis, or an individual exhibiting clinical symptoms."); *see also* Ex. 1003 at 7:9-13 ("As can be seen from the dosage regimes, the amount of methotrexate administered is to be sufficient to relieve the autoimmune disease symptoms prevalent in diseases such as arthritis and psoriasis."); *see also* Gershwin Decl. (Ex. 1012) at ¶ 56.
subcutaneously administering to said patient a medicament comprising methotrexate	Grint teaches subcutaneous administration. Ex. 1003 at 5:64 ("Methotrexate may also be administered parenterally. …"); *see also* Ex. 1003 at 7:56-57 ("The dose of MTX was 12.5-25 mg/week (oral, subcutaneous, or Intramuscular. …"); *see also* Ex. 1003 at 8:1-2 ("MTX (oral/intramuscular/SC)…."); *see also*

	Gershwin Decl. (Ex. 1012) at ¶ 57.
in a pharmaceutically acceptable solvent at a concentration of more than 30 mg/ml.	Grint teaches MTX solutions that are suitable for administration to patients at concentrations of more than 30 mg/ml. Ex. 1003 at 6:66-7:1 ("Expressed in proportions, methotrexate is generally present in from about 0.1 to 40 mg/ml of carrier"); *see also* Ex. 1003 at 6:3-6: ("The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions. … The carrier can be a solvent or dispersion medium containing, for example, water, ethyl alcohol, polyol …, suitable mixtures thereof, and vegetable oils."); *see also* Gershwin Decl. (Ex. 1012) at ¶¶ 58-59.
Claim 2. The method according to claim 1, wherein the methotrexate is present at a concentration of more than 30 mg/ml to 100 mg/ml.	*See, supra*, at claim 1.
Claim 4. The method according to claim 1, wherein the pharmaceutically acceptable solvent is selected from water, water for injection purposes, water comprising isotonization additives and sodium chloride solution.	Grint teaches that the pharmaceutically acceptable solvents can include water and sodium chloride. Ex. 1003 at 6:11-15 ("The carrier can be a solvent or dispersion medium containing … water, ethyl alcohol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol and the like), suitable mixtures thereof, and vegetable oils."); *see also* Ex. 1003 at 6:22-24 ("In many cases, it will be preferable to include isotonic agents, for

	example, sugars or sodium chloride."); *see also* Gammon Decl. (Ex. 1013) at ¶ 47.
Claim 5. The method according to claim 1, 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.	Grint teaches treatment of at least rheumatoid arthirits, psoriasis, and multiple sclerosis. Ex. 1003 at 1:12-15 ("The invention relates to a method for controlling autoimmune diseases, such as rheumatoid arthritis, inflammatory bowel disease, multiple sclerosis and psoriasis."); *see also* Ex. 1003 at 3:4-9 ("The methods of the invention can be used prophylactically or for treatment of established autoimmune disease."); *see also* Ex. 1003 at 7:9-13 ("As can be seen from the dosage regimes, the amount of methotrexate administered is to be sufficient to relieve the autoimmune disease symptoms prevalent in diseases such as arthritis and psoriasis."); *see also* Gershwin Decl. (Ex. 1012) at ¶ 63.
Claim 6. The method according to claim 5, wherein the inflammatory autoimmune disease is rheumatoid arthritis.	*See, supra*, at claim 5.
Claim 11. The method according to claim 1, wherein the medicament is contained in a storage container.	Grint teaches MTX in a storage container. Ex. 1003 at 6:52-59 ("It is especially advantageous to formulate parenteral compositions in dosage unit form. … Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the

	mammalian subjects to be treated; each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier."); *see also* Gammon Decl. (Ex. 1013) at ¶ 45.
Claim 12. The method according to claim 11, wherein the storage container contains a total dosage amount of 5 to 5,000 mg.	Grint teaches total dosage amounts of MTX between 5 and 5,000 mg. Ex. 1003 at 6:52-66 ("A unit dosage form can, for example, contain methotrexate in amounts ranging from about 0.1 to 400 mg, with from 1 to 35 mg being preferred, and 10 to 25 being most preferred."); *see also* Gammon Decl. (Ex. 1013) at ¶¶ 45-46.
Claim 13. The method according to claim 11, wherein the storage the storage container is an injection bottle, a vial, a bag, a glass ampoule, or a capsule.	Grint teaches that MTX can be in a dosage unit form containing MTX. A "dosage unit form" containing MTX would include an injection bottle, vial, bag, glass ampule, or carpule. Gammon Decl. (Ex. 1013) at ¶ 45.
Claim 17. The method according to claim 4, wherein the sodium chloride solution is isotonic sodium chloride solution.	Grint teaches that the sodium chloride solution may be isotonic. Ex. 1003 at 6:22-24 ("In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride."); *see also* Gammon Decl. (Ex. 1013) at ¶ 47.
Claim 22. The method according to claim 1, wherein the methotrexate is present at a concentration of from 40 mg/ml to 80 mg/ml.	Grint teaches concentrations of MTX between 40 and 80 mg/ml. Ex. 1003 at 6:66-7:1 ("Expressed in proportions, methotrexate is generally present

	in from about 0.1 to 40 mg/ml of carrier"); *see also* Gershwin Decl. (Ex. 1012) at ¶ 66.

B. Ground 2: Claims 7-10, 14-16, and 19-21 are obvious over U.S. Patent No. 6,554,504 (Grint, Ex. 1003) in view of Insulin Admin. (Ex. 1015).

As discussed above, Grint (Ex. 1003) teaches methods for treating inflammatory autoimmune diseases via subcutaneous injections of MTX at concentrations greater than 30 mg/ml. Grint does not expressly disclose MTX packaged in forms suitable for self-administration, or injection devices such as ready-made syringes and pen-injectors. These elements, however, were well known in the art prior to 2006.

Receiving injections would require a patient to travel to a clinic to allow the medical staff to prepare the drug and administer the injection. This was inconvenient, time consuming and costly for both the patient and clinic. Gammon Decl. (Ex. 1013) at ¶ 50. Self-administration of injectable drugs, via injection devices such as ready-made syringes and pen-injectors, resolved this problem as it eliminated the need for a patient to visit a clinic to receive his or her medication. *Id*. at ¶ 50; Gershwin Decl. (Ex. 1012) at ¶ 33. Insulin Admin., published in 1993, and thus prior art to the '231 Patent, discloses the use of an "pen" and "prefilled syringe" for the self-administration of insulin. Ex. 1015 at S121, 123.

More specifically, Insulin Admin. states that "[w]henever possible, insulin should be self-administered by the patient." *Id*. at S124. Insulin Admin. achieves self-administration by using either a "pen-like device" or a "prefilled syringe." *Id*. at S123. Insulin Admin.'s "pen-like device" is the same as the claimed "pen injector" of the '231 Patent, and also constitutes the "injection device" claimed in claim 8 of the '231 patent. Gammon Decl. (Ex. 1013) at ¶ 51. Moreover, Insulin Admin.'s disclosure of a "prefilled syringe" meets the "ready-made syringe" limitation recited in claim 10 of the '231 Patent. Gammon Decl. (Ex. 1013) at ¶ 52. The '231 Patent also makes clear that it was routine in the art as of 2006 to formulate injectable drugs such as methotrexate into ready-made syringes and injection devices/pen-injectors in order to allow for self-administration, and to increase patient compliance and comfort. Ex. 1001 at 2:26-36; 6:54-61 ("[r]eady-made syringes for parenteral administration containing methotrexate solutions … **are known from the prior art**…;" "[s]uch injection devices are well known in the art. Preferably, one such injection device is a so-called pen injector.") (emphasis added); *see also* Gammon Decl. (Ex. 1013) at ¶¶ 49-54.

Accordingly, it would have required no more than routine effort for those skilled in the art to combine the teachings of Grint with the disclosure of Insulin Admin. to arrive at a concentrated MTX solution that can be self-administered by

means of an injection device, ready-made syringe, or pen-injector. Gammon Decl. (Ex. 1013) at ¶ 54. Indeed, as acknowledged by the '231 Patent, the existence of injection devices containing methotrexate (including ready-made syringes) would have motivated a skilled artisan to combine Grint with Insulin Admin. Moreover, there would have been nothing unpredictable or unexpected regarding the development of the claimed ready-made syringes and injection devices/pen injectors because Insulin Admin. teaches that they are marketed as of 2003. Gammon Decl. (Ex. 1013) at ¶ 51-54. Thus, Grint, combined with Insulin Admin. teaches each and every element of claims 7-10, 14-16, and 19-21, thus making these claims invalid under 35 U.S.C. § 103(a).

1. Ground 2 Claim Chart

Claim	Grint and Insulin Admin.
Claim 7. The method according to claim 1, wherein the medicament is present in a form suitable for patient self-administration.	*See, supra*, Section XII.A.1., claim 1 analysis and Grint. Ex. 1015 at S121 ("This position statement addresses issues regarding use of conventional insulin administration (i.e., via syringe or pen with needle and cartridge) in the self-care of the individual with diabetes."); *see also* Ex. 1015 at S124 ("Whenever possible, insulin should be self-administered by the patient."); *see also* Ex. 1015 at S124 ("[t]he syringes may be

	prefilled periodically by a relative, friend, home health aide, or visiting nurse and the dose may be self injected."); *see also* Gammon Decl. (Ex. 1013) at ¶¶ 51-54.
Claim 8. The method according to claim 1, wherein the medicament is contained in an injection device for a single application.	Ex. 1015 at S123 ("Several pen-like devices and insulin-containing cartridges are available that deliver insulin subcutaneously through a needle."); *see also* Gammon Decl. (Ex. 1013) at ¶¶ 51-54.
Claim 9. The method according to claim 8, wherein the injection device contains a dosage of 5 to 40 mg of methotrexate.	See above for claim 8; *see also* *Supra*, Section XII.A.1. for claim 12, showing exemplary support in Grint.
Claim 10. The method according to claim 8 or 9, wherein the injection device is a ready-made syringe.	Ex. 1015 at S123 ("Several pen-like devices and insulin-containing cartridges are available that deliver insulin subcutaneously through a needle."); *see also* Ex. 1015 at S123 "Some individuals may benefit from the use of prefilled syringes (e.g., the visually impaired, those dependent on others for drawing their insulin, or those traveling or eating in restaurants."); *see also* Gammon Decl. (Ex. 1013) at ¶¶ 51-54.
Claim 14. The method according to claim 13, wherein the storage container is a carpule and wherein said carpule is suitable for administering the medicament by means of an injection device.	Ex. 1015 at S123 ("Several pen-like devices and insulin-containing cartridges are available that deliver insulin subcutaneously through a needle."); *see also* Gammon Decl. (Ex. 1013) at ¶¶ 45 and 49-54.
Claim 15. The method	Ex. 1015 at S123 ("Several pen-like devices

according to claim 14, wherein the carpule and the pen injector are provided such that multiple applications of single dosages can be administered.	and insulin-containing cartridges are available that deliver insulin subcutaneously through a needle. In many patients (e.g., especially those who are neurologically impaired and those using multiple daily injection regimes), these devices have been demonstrated to improve accuracy of insulin administration and/or adherence."); *see also* Gammon Decl. (Ex. 1013) at ¶¶ 49-54.
Claim 16. The method according to claim 15, wherein the single dosages per application can be adjusted to 5 to 40 mg each of methotrexate.	See above for claim 15; *see also* *Supra*, Section XII.A.1. for claim 12, showing exemplary support in Grint.
Claim 19. The method according to claim 9, wherein the injection device contains a dosage selected from 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.	See above for claim 15; *see also* *Supra*, Section XII.A.1. for claim 12, showing exemplary support in Grint.
Claim 20. The method according to claim 14, wherein the injection device is a pen injector.	Ex. 1015 at S123 ("Several pen-like devices and insulin-containing cartridges are available that deliver insulin subcutaneously through a needle."); *see also* Gammon Decl. (Ex. 1013) at ¶¶ 49-54.
Claim 21. The method according to claim 16, wherein the single dosages of methotrexate per application is adjusted to be 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.	See above for claim 15; *see also* *Supra*, Section XII.A.1. for claim 12, showing exemplary support in Grint.

C. Ground 3: Claim 18 is obvious over U.S. Patent No. 6,554,504 (Grint, Ex. 1003) in view of Alsufyani (Ex. 1006).

Claim 18, which recites that the rheumatoid arthritis of claim 6 is "juvenile rheumatoid arthritis" ("jRA") is obvious in light of primary reference Grint (Ex. 1003) for all of the reasons discussed above, and further in view of Alsufyani (Ex. 1006). Grint teaches the use of highly concentrated solutions of MTX to treat RA. Ex. 1003 at 2:23-24; 3:4-5; 5:64; 6:66-7:1; 7:56-57. A person of ordinary skill in the art would understand Grint's disclosure of RA to include jRA, as MTX was widely used to treat jRA prior to 2006. Gershwin Decl. (Ex. 1012) at ¶¶ 67-70. Moreover, Alsufyani teaches that subcutaneously delivered methotrexate is an effective therapy for jRA patients. Ex. 1006 at 179, Abstract ("Objective. To describe the outcome of patients with juvenile idiopathic arthritis (JIA) treated with subcutaneous (SC) methotrexate (MTX). … Conclusion. … the use of SC MTX has a high likelihood of success with more than 70% of patients achieving clinically significant improvement, without clinically significant toxicity."); Gershwin Decl. (Ex. 1012) at ¶¶ 68-69. Alsufyani was published in 2004, and is pre-AIA § 102(b) art. Accordingly, because Grint teaches that concentrated MTX solutions can be successfully used to treat RA, one of ordinary skill in the art would have been motivated, with a reasonable expectation of success, to combine the teachings of Grint and Alsufyani to use highly concentrated solutions of MTX

for the treatment of RA, rendering claim 18 unpatentable under 35 U.S.C. §103(a). Gershwin Decl. (Ex. 1012) at ¶ 70.

1. Ground 3 Claim Chart

Claim	Grint and Alsufyani.
Claim 18. The method according to claim 6, wherein rheumatoid arthritis is juvenile rheumatoid arthritis.	Alsufyani teaches MTX may be used subcutaneously to treat juvenile rheumatoid arthritis. *See, supra*, Section XII.A.1., claims 1, 5, and 6, analyses based on Grint. Ex. 1006 at 179, first paragraph ("Methotrexate (MTX) is an effective agent in the treatment of juvenile idiopathic arthritis (JIA)."); *see also* Ex. 1006 at 179, Abstract ("Objective. To describe the outcome of patients with juvenile idiopathic arthritis (JIA) treated with subcutaneous (Sc) methotrexate (MTX)….Conclusion.…the use of SC MTX has a high likelihood of success with more than 70% of patients achieving clinically significant improvement, without clinically significant toxicity."); *see also* Gershwin Decl. (Ex. 1012) at ¶¶ 67-70.

D. Grounds 4 and 5: Claims 1-5, 7-17, and 19-22 are obvious under pre-AIA 35 U.S.C. § 103(a) over primary references PDR (Ex. 1007) or Hospira (Ex. 1009) and Brooks (Ex. 1008), in further view of Insulin Admin. (Ex. 1015) and Alsufanyi (Ex. 1006).

1. Discussion of the primary references

a. The primary reference PDR teaches MTX at concentrations between 2 and 125 mg/ml for intramuscular injection to treat psoriasis.

The PDR (Exhibit 1007; comprising pages 762-764 from the 1985 edition of the Physician's Desk Reference) is prior art to the '231 Patent under pre-AIA § 102(b). The PDR is published annually, and compiles package inserts for FDA-approved drugs. Gershwin Decl. (Ex. 1012) at ¶ 71; Gammon Decl. (Ex. 2013) at ¶ 55. The provided PDR pages comprise a reprint of the "full text of the latest Official Package Circular dated July 1984" for the product "Mexate®…(methotrexate sodium) FOR INJECTION." Ex. 1007 at 762, middle col. The PDR for Mexate® was not considered by the Examiner during prosecution of the '231 Patent.

The PDR teaches that the product Mexate® was available in 1984 for intramuscular injection to treat psoriasis. *Id*. at 764, middle col. The package insert provides that vials containing 20, 50, 100, or 250 mg of MTX were available, and instructs reconstituting these vials with "2 to 10 mls" of sterile water or sodium chloride. *Id*. Reconstituting the available 20, 50, 100, or 250 mg vials with 2 mLs of diluent would result in a MTX solution having a concentration of 10, 25, 50, and 125 mg/ml, respectively. Gammon Decl. (Ex. 1013) at ¶ 57. Reconstituting the available 20, 50, 100, or 250 mg vials with 10 mLs of diluent would result in a MTX solution having a concentration of 2, 5, 10, and 25 mg/ml, respectively. *Id*.

Further, because the PDR is the FDA approved label, the manufacturer must have established that administering doses of MTX taken from MTX solutions with concentrations of between 2-125 mg/ml was safe and effective. Gershwin Decl. (Ex. 1012) at ¶ 73; Gammon Decl. (Ex. 1013) at ¶ 57. Moreover, the PDR discloses that the toxicity associated with MTX therapy "is usually dose related." Ex. 1007 at 763. Thus, one of skill in the art would understand from the PDR for Mexate® that a higher concentrated MTX solution can be used to treat psoriasis, so long physicians monitor the dose. Gershwin Decl. (Ex. 1012) at ¶ 74. Accordingly, the PDR teaches MTX solutions having concentrations between 2 and 125 mg/ml, including 50 mg/ml, for intramuscular administration to treat psoriasis.

b. The primary reference Hospira teaches 100 mg/ml MTX for intramuscular injection to treat psoriasis

Exhibit 1009 ("Hospira") is a printed package insert for a methotrexate product sold by Hospira UK Ltd., which is dated November 22, 2005, and is prior art to the '231 Patent. A related document, which comprises the first page of a 1994 version of the package insert for the Hospira product, was submitted to the USPTO during prosecution of the '231 Patent, but Exhibit 1009 was not. *See* Ex. 1001 at front cover "References Cited", showing the package insert page as submitted to the USPTO. The Hospira reference, and its related predecessor, was not cited as a basis for any rejection during prosecution of the '231 Patent.

Hospira describes the product as "Methotrexate 100 mg/ml Injection," and thus discloses a 100 mg/ml concentration of MTX. Ex. 1009 at § 1 "Trade Name of the Medicinal Product;" § 2 "Qualitative and Quantitative Composition." Hospira also discloses that the 100 mg/ml MTX solution can be used to treat "severe recalcitrant disabling psoriasis." *Id*. at § 4.1 "Therapeutic Indications." Finally, Hospira discloses that the 100 mg/ml concentration of MTX can be administered by the intramuscular route. *Id*. While Hospira warns against using certain MTX concentrations for intrathecal administration (injections into the spine) (*id*. at § 4.4 "Special warnings and precautions for use: Precautions"), it does not caution against using the highly concentrated MTX solutions for intramuscular injections. Thus, the package insert describes a 100 mg/ml solution of MTX for intramuscular injection to treat psoriasis. Gershwin Decl. (Ex. 1012) at ¶ 77; Gammon Decl. (Ex. 1013) at ¶¶ 63-66.

c. The primary reference Brooks (Ex. 1008) teaches that intramuscular and subcutaneous injections of MTX are interchangeable

Neither the PDR nor Hospira expressly recite subcutaneous administration. However, Brooks (Ex. 1008) supplies this teaching. Brooks was published in 1990 and is prior art to the '231 Patent. Brooks was cited and consider by the Examiner during prosecution of the '231 Patent. Ex. 1002 at 14. The Examiner did not,

however, use Brooks as a basis for any rejection. As demonstrated below, a skilled artisan would have been motivated to combine the PDR or Hospira with Brooks in an effort to provide suitable options for parenteral MTX administration, with a reasonable expectation of success.

Brooks reports that in 1990, "the intramuscular route [of administering MTX] is a desirable choice for parenteral drug administration because of the completeness of absorption relative to the oral route, peak concentrations that are similar to those achieved using the IV route, and slower drug absorption and prolonged exposure to the drug compared with IV administered MTX." Ex. 1008 at 91; Gershwin Decl. (Ex. 1012) at ¶ 80. As a predicate for his reported study, Brooks states that "subcutaneous (SQ) injections may also exhibit these beneficial pharmacokinetic patterns and would have the potential advantages of patient self-administration at home and greater patient comfort than with weekly IM injections given in the physician's office." Ex. 1008 at 91; Gershwin Decl. (Ex. 1012) at ¶ 80. Intramuscular injections are painful and most often must be administered by physicians or staff in the hospital or physician's office. Gershwin Decl. (Ex. 1012) at ¶ 80.

Brooks then reports on a study comparing serum concentrations and the pharmacokinetic parameters of MTX after intramuscular and subcutaneous

administration in patients with RA. Ex. 1008 at 93; Gershwin Decl. (Ex. 1012) at ¶ 81. Brooks found that the "pharmacokinetic parameters are similar for these 2 routes of administration," and concludes that "IM and SQ are interchangeable routes of administration." Ex. 1008 at 93 (emphasis added); Gershwin Decl. (Ex. 1012) at 81. In other words, Brooks established that subcutaneously administered MTX is bioequivalent to intramuscularly administered MTX. Gershwin Decl. (Ex. 1012) at 81. Brooks adds that "SQ administration may be a more convenient and less painful way of administering [methotrexate]." Ex. 1008 at 91. Thus, Brooks teaches that the subcutaneous and intramuscular routes of administering MTX are interchangeable, and subcutaneous administration may be preferred due to patient preference and convenience. Persons of ordinary skill in the art at least as of Brooks' 1990 publication date also knew that subcutaneous administration of MTX was more preferable than intramuscular administration due to reduced pain. Gershwin Decl. (Ex. 1012) at ¶¶ 83-84.

2. Ground 4: Claims 1-5, 11-13, 17, and 22 are obvious over the PDR (Ex. 1007) or Hospira, (Ex. 1009) in view of Brooks (Ex. 1008)

As reaffirmed by the Supreme Court in *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398 (2007) ("KSR"), the framework for the objective analysis for determining obviousness under pre-AIA 35 U.S.C. § 103 is stated in *Graham v.*

John Deere Co., 383 U.S. 1 (1966) ("Graham"). The Graham factors, which include (A) determining the scope and content of the prior art; (B) ascertaining the differences between the claimed invention and the prior art; and (C) resolving the level of ordinary skill in the pertinent art, are the controlling inquiries in any obviousness analysis. *KSR*, 550 U.S. at 406-07 (2007).

As explained above, and as supported by the Declarations of Dr. Gershwin and Mr. Gammon, the PDR and Hospira teach treatment of psoriasis, an inflammatory autoimmune disease, with intramuscular injections of MTX having concentrations as high as 125 mg/ml, *see supra* at § XII.D.1(a-b). Brooks (Ex. 1008) teaches that intramuscular and subcutaneous routes of MTX administration are interchangeable. Ex. 1008 at 93; Gershwin Decl. (Ex. 1012) at ¶ 83. The skilled artisan reading these references in 2006 would have understood that the concentrations described in the PDR and Hospira could be administered subcutaneously. Gershwin Decl (Ex. 1012) at ¶ 84. Indeed, nothing in the PDR, Hospira or Brooks cautions against using highly concentrated MTX solutions subcutaneously for the treatment of inflammatory autoimmune diseases. Gershwin Decl. (Ex. 1012) at ¶ 84; Gammon Decl. (Ex. 1013) at ¶¶ 65-66.

The skilled artisan would have been motivated to use the concentrated MTX solutions described in the PDR or Hospira subcutaneously because Brooks taught

that subcutaneously and intramuscularly administered methotrexate were "interchangeable routes of administration," and because "SQ administration may be a more convenient and less painful way of administering [methotrexate]."[2] Ex. 1008 at 93; Gershwin Decl. (Ex. 1012) at ¶ 81-84. Further, it was well known prior to 2006 that subcutaneous administration was desirable because it is less painful than intramuscular administration and patients could self-administer subcutaneously in the convenience of their home. Gershwin Decl. (Ex. 1012) at ¶ 82. Thus, the skilled artisan would have expected that administering the highly concentrated MTX solutions disclosed the PDR or Hospira subcutaneously would produce the same results as administering them intramuscularly. Gershwin Decl. (Ex. 1012) at ¶¶ 82-84.

Claims 1-5, 11-13, 17, and 22 of the '231 Patent should thus be canceled as obvious under 35 U.S.C. § 103(a).

[2] The Zackheim reference, which was cited during prosecution of the '231 Patent, cited Brooks for the proposition that intramuscular and subcutaneous administration of MTX were interchangeable. *See* Ex. 1010 at 1008, left column, 3rd ¶.

a. Claim chart for Ground 4 showing exemplary citations in PDR and Brooks

Claim	PDR and Brooks
Claim 1. A method for the treatment of inflammatory autoimmune diseases in a patient in need thereof, comprising	The PDR teaches MTX to treat an inflammatory autoimmune disease. Ex. 1007 at 764, middle column ("Psoriasis…Directions for Use: Intramuscular or intravenous administration"); *see also* Gershwin Decl. (Ex. 1012) at ¶ 72. Brooks also teaches treatment of rheumatoid arthritis, an inflammatory autoimmune disease. Ex. 1008 at 91 ("Methotrexate (MTX), a folic acid antagonist, has recently been approved by the Food and Drug Administration for use in patients with severe rheumatoid arthritis that is refractory to conventional therapy."); *see also* Gershwin Decl. (Ex. 1012) at ¶ 78.
subcutaneously administering to said patient a medicament comprising methotrexate	Brooks teaches subcutaneous administration of MTX. Ex. 1008 at 91 ("The serum concentrations and the pharmacokinetics of low-dose methotrexate (MTX) were compared after both intramuscular (IM) and subcutaneous (SQ) injections in 5 patients with rheumatoid arthritis"; *see also* Ex. 1008 at Abstract ("IM and SQ are interchangeable routes of administration"; *see*

	also Gershwin Decl. (Ex. 1012) at ¶ 80.
in a pharmaceutically acceptable solvent at a concentration of more than 30 mg/ml.	The PDR teaches MTX in a pharmaceutically acceptable solvent at concentrations greater than 30 mg/ml. Ex. 1007 at 764, middle column ("Directions for Use: … reconstitute with 2 to 10 ml of Sterile Water for Injection, USP, 0.9% Sodium Chloride Injection, USP…."); *see also* Ex. 1007 at 764, last column ("How Supplied: Mexate … 20 mg vial … 50 mg vial … 100 mg vial … 250 mg vial.") [note that reconstituting these vials with the 2 to 10 ml as noted above results in 2 mg/ml, 5 mg/ml, 10 mg/ml, 25 mg/ml, 50 mg/ml, and 125 mg/ml]; *see also* Gershwin Decl. (Ex. 1012) at ¶ 73; *see also* Gammon Dec. (Ex. 1013) at ¶ 59.
Claim 2. The method according to claim 1, wherein the methotrexate is present at a concentration of more than 30 mg/ml to 100 mg/ml.	*See, supra*, at claim 1.
Claim 3. The method according to claim 2, wherein the methotrexate is present at a concentration of about 50 mg/ml.	*See, supra*, at claim 1.
Claim 4. The method according to claim 1, wherein the pharmaceutically acceptable solvent is selected from water, water for	The PDR teaches MTX in a pharmaceutically acceptable solvent that is water or sodium chloride. Ex. 1007 at 764, middle column ("Directions

injection purposes, water comprising isotonization additives and sodium chloride solution.	for Use: … reconstitute with 2 to 10 ml of Sterile Water for Injection, USP, 0.9% Sodium Chloride Injection, USP….”); *see also* Gammon Decl. (Ex. 1013) at ¶ 58.
Claim 5. The method according to claim 1, 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.	The PDR teaches administering MTX to treat psoriasis. Ex. 1007 at 764, middle column (“Psoriasis”); *see also* Gershwin Decl. (Ex. 1012) at ¶ 72.
Claim 11. The method according to claim 1, wherein the medicament is contained in a storage container.	The PDR teaches MTX in a storage container. Ex. 1007 at 764, last column (“How Supplied: Mexate…20 mg vial…50 mg vial…100 mg vial…250 mg vial.”).; *see also* Gammon Dec. (Ex. 1013) at ¶ 57.
Claim 12. The method according to claim 11, wherein the storage container contains a total dosage amount of 5 to 5,000 mg.	The PDR teaches MTX in a storage container containing doses of MTX between 5 mg and 5,000 mg. Ex. 1007 at 764, last column (“How Supplied: Mexate … 20 mg vial … 50 mg vial … 100 mg vial … 250 mg vial.”); *see also* Gammon Dec. (Ex. 1013) at ¶ 57.
Claim 13. The method according to claim 11, wherein the storage the	The PDR teaches MTX in vial. Ex. 1007 at 764, last column (“How

storage container is an injection bottle, a vial, a bag, a glass ampoule, or a capsule.	Supplied: Mexate … 20 mg vial … 50 mg vial … 100 mg vial … 250 mg vial."); *see also* Gammon Dec. (Ex. 1013) at ¶ 59.
Claim 17. The method according to claim 4, wherein the sodium chloride solution is isotonic sodium chloride solution.	The PDR teaches MTX in a isotonic sodium chloride solution. Ex. 1007 at 764, middle column ("Directions for Use: … reconstitute with 2 to 10 ml of Sterile Water for Injection, USP, 0.9% Sodium Chloride Injection, USP…."); *see also* Gammon Decl. (Ex. 1013) at ¶ 57.
Claim 22. The method according to claim 1, wherein the methotrexate is present at a concentration of from 40 mg/ml to 80 mg/ml.	*See, supra*, at claim 1.

b. Claim chart for Ground 4 showing exemplary citations in Hospira and Brooks

Claim	Hospira and Brooks
Claim 1. A method for the treatment of inflammatory autoimmune diseases in a patient in need thereof, comprising	Hospira teaches administering MTX to treat an inflammatory autoimmune disease. Ex. 1009 at 4.1 ("Methotrexate is indicated in the treatment of…psoriasis…."); *see also* Gershwin Decl. (Ex. 1012) at ¶ 76. Brooks also teaches treatment of rheumatoid arthritis, an inflammatory autoimmune disease.

	Ex. 1008 at 91 ("Methotrexate (MTX), a folic acid antagonist, has recently been approved by the Food and Drug Administration for use in patients with severe rheumatoid arthritis that is refractory to conventional therapy."); see also Gershwin Decl. (Ex. 1012) at ¶ 78.
subcutaneously administering to said patient a medicament comprising methotrexate	Brooks teaches subcutaneous administration of MTX. Ex. 1008 at 91 ("The serum concentrations and the pharmacokinetics of low-dose methotrexate (MTX) were compared after both intramuscular (IM) and subcutaneous (SQ) injections in 5 patients with rheumatoid arthritis"; *see also* Ex. 1008 at Abstract ("IM and SQ are interchangeable routes of administration"; *see also* Gershwin Decl. (Ex. 1012) at ¶ 80.
in a pharmaceutically acceptable solvent at a concentration of more than 30 mg/ml.	Hospira teaches MTX in a pharmaceutically acceptable solvent at concentrations greater than 30 mg/ml. Ex. 1009 at 1 ("Methotrexate 100 mg/ml Injection"); *see also* Gershwin Decl. (Ex. 1012) at ¶ 76; *see also* Gammon Dec. (Ex. 1013) at ¶ 63.
Claim 2. The method according to claim 1, wherein the methotrexate is present at a concentration of more than 30 mg/ml to 100 mg/ml.	*See, supra*, at claim 1.
Claim 3. The method	*See, supra*, at claim 1.

according to claim 2, wherein the methotrexate is present at a concentration of about 50 mg/ml.	
Claim 4. The method according to claim 1, wherein the pharmaceutically acceptable solvent is selected from water, water for injection purposes, water comprising isotonization additives and sodium chloride solution.	Hospira teaches MTX in a pharmaceutically acceptable solvent that is water or sodium chloride. Ex. 1009 at 6.1("List of excipients … water…."); *see also* Gammon Decl. (Ex. 1013) at ¶ 63.
Claim 5. The method according to claim 1, 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.	Hospira teaches administering MTX to treat psoriasis. Ex. 1009 at 4.1 ("Methotrexate is indicated in the treatment of…psoriasis…."); *see also* Gershwin Decl. (Ex. 1012) at ¶ 76.
Claim 11. The method according to claim 1, wherein the medicament is contained in a storage container.	Hospira teaches MTX in a storage container. Ex. 1009 at 6.3 ("After dilution … in containers. …); *see also* Gammon Dec. (Ex. 1013) at ¶¶ 63-64.
Claim 12. The method according to claim 11, wherein the storage container contains a total dosage amount of 5 to 5,000 mg.	Hospira teaches MTX in a storage container containing 1 gram and 5 grams of MTX, which is equal to 1000 mg and 5000 mg, respectively. Ex. 1009 at 6.5 ("1 g/10 mls … 5g/50 mls …"); *see also*

	Gammon Decl. (Ex. 1013) at ¶ 63-64.
Claim 13. The method according to claim 11, wherein the storage the storage container is an injection bottle, a vial, a bag, a glass ampoule, or a capsule.	Hospira teaches MTX in vial. Ex. 1009 at 6.5 ("1 g/10 mls … vial … 5g/50mls … vial…."); *see also* Gammon Decl. (Ex. 1013) at ¶¶ 63-64.
Claim 17. The method according to claim 4, wherein the sodium chloride solution is isotonic sodium chloride solution.	Hospira teaches an isotonic sodium chloride solution. Gammon Decl. (Ex. 1013) at ¶ 63.
Claim 22. The method according to claim 1, wherein the methotrexate is present at a concentration of from 40 mg/ml to 80 mg/ml.	*See, supra,* at claim 1.

3. Ground 5: Claims 7-10, 14-16, and 19-21 are obvious over PDR (Ex. 1007) or Hospira (Ex. 1009) and Brooks (Ex. 1008), in view of Insulin Admin. (Ex. 1015)

As discussed above, the combination of PDR or Hospira and Brooks teach methods for treating inflammatory autoimmune diseases via subcutaneous injections of MTX at concentrations greater than 30 mg/ml. See §XII.D.2, *supra*. These primary references do not expressly disclose MTX packaged in forms suitable for self-administration, ready-made syringes, or injection devices such as pen-injectors. But as discussed above in § XII.B, Insulin Admin. discloses that such injection devices were available for delivering injectable medicaments. Ex. 1015 at S123-24; Gammon Decl. (Ex. 1013) at ¶ 51. Accordingly, one of ordinary

skill in the art would be motivated, with a reasonable expectation of success, to combine the references and package a highly concentrated MTX solution in an injection device, ready-made syringe, and/or pen injector because it would aid patient compliance by allowing for easier, self-administration of the MTX solution. Gammon Decl. (Ex. 1013) at ¶ 54. This Ground is further reinforced by the fact that the '231 Patent acknowledges that injection devices, such as ready-made syringes and pen-injectors, were well-known prior to 2006. Gammon Decl. (Ex. 1013) at ¶ 14. Thus, the combination of the PDR or Hospira, Brooks and Insulin Admin. teaches each and every element of claims 7-10, 14-16, and 19-21, and therefore these claims should be found unpatentable under 35 U.S.C. §103(a).

The Board is referred to §§ XII.B and D detailing the exemplary citations in the PDR, Hospira, Brooks, and Insulin Admin., respectively, for each and every element of claims 7-10, 14-16, and 19-21.

XIII. Secondary Considerations Do Not Rebut the *Prima Facie* Case of Obviousness

Objective indicia of non-obviousness ("secondary considerations") must be considered in an obviousness determination. *See, e.g.*, *Ruiz v. A.B. Chance Co.*, 234 F.3d 654, 667 (Fed. Cir. 2000). Such secondary considerations can include evidence of unexpected results and evidence that the prior art taught away from the claimed invention in any material respect. During prosecution of the '231 Patent,

Applicant presented arguments of unpredictability, unexpected results, and teaching away to support the patentability of the application. None of these arguments, and none of the "evidence" cited by Applicant, rebuts Petitioner's prima facie case of obviousness. Tellingly, the Applicant declined to repeat their alleged indicia of non-obviousness during the '091 IPR.

A. Any toxicity associated with MTX after subcutaneous injection is dose–not concentration–dependent.

Applicant argued during prosecution that highly concentrated solutions of MTX were used "solely" to treat cancer[3], and that "persons skilled in the art would have been very cautious to increase the concentration of the active agent in a subcutaneously administered solution" because it would not have been obvious that toxicity of MTX solutions with higher concentrations would be acceptable. Ex. 1002 at 21, 3/21/12 OA Response. However, such assertions were not accompanied by any evidentiary support and are contradicted by the prior art.

Toxicity associated with MTX is dose – not concentration – dependent, and the same dose of MTX is administered regardless of concentration. Gershwin Decl. (Ex. 1012) at ¶ 87. For example, the PDR cautions that doses of "50 mg per week should ordinarily not be exceeded," and that "Mexate has a high potential for

[3] As discussed in § XII.D.1.b, Hospira teaches injecting concentrated MTX solutions for the treatment of psoriasis.

serious toxicity which is usually dose-related." Ex. 1007 at 763 (emphasis added). Hospira states similar precautions. Ex. 1009 at § 4.4 ("[m]ethotrexate has a high potential toxicity, usually dose related…."); *id*. ("when such [toxic] effects or reactions do occur, the drug should be reduced in dosage. …"). Moreover, peer-reviewed publications prior to 2006 acknowledge the dose-dependency nature of MTX toxicity. For example, Weinblatt 1993 discloses that "the most common adverse event with methotrexate is gastrointestinal toxicity, including anorexia, nausea, vomiting, diarrhea, and weight loss," and that this toxicity "may improve with dose reduction. …" Ex. 1018 at 774 "Toxicity." Thus, any toxicity related to administration of MTX is clearly dose dependent, not concentration dependent. Gershwin Decl. (Ex. 1012) at ¶¶ 87-92.

Additionally, the PDR and Hospira each establish that prior to 2006, MTX at concentrations greater than 30 mg/ml was available and recommended for intramuscular administration to treat psoriasis, an inflammatory autoimmune diseases. Ex. 1007 at 764; Ex. 1009 at § 4.1 "Therapeutic Indications"; Gershwin Decl. (Ex. 1012) at ¶¶ 72-74 and 76-77. These concentrations would also have been safe for subcutaneous injection, particularly in view of Brooks, which teaches that subcutaneous and intramuscular injections are "interchangeable routes of administration," and that "SQ administration may be a more convenient and less

painful way of administering [methotrexate].” Ex. 1008 at 91; Gershwin Decl. (Ex. 1012) at ¶¶ 78-82. Indeed, Brooks expressed no concern, warning, or belief that the concentration of MTX would alter his conclusion that subcutaneous and intramuscular routes are interchangeable. *Id*. The skilled artisan in 2006 would have read Brooks and concluded that the highly concentrated MTX solutions described in the PDR and Hospira could be administered subcutaneously without raising issues of toxicity or bioavailability. Gershwin Decl.(Ex. 1012) at ¶ 84.

Moreover, MTX was known as of the priority date to have a “well-defined toxicity profile,” to be effective over long periods “with considerably lower toxicity than previously available [disease-modifying anti-rheumatoid drugs],” and to “have very few clinically significant side effects.” Ex. 1014 at S-180-181; Ex. 1018 at 774-76. Indeed, a study published by Hoffmeister et al. in 1983, reported the results of 15 years of treating patients with up to 15 mg/ml of MTX given intramuscularly or orally. Hoffmeister 1983 (Ex. 1019) at 70. The report concluded that low dose MTX for rheumatoid arthritis is both effective and free of serious side effects. *Id*. at Abstract; Gershwin Decl. (Ex. 1012) at ¶ 29. Although dose-related toxicity was noted and of some concern, physicians were well equipped with methods to monitor and control such adverse events. *Id*. at ¶ 37; Ex. 1018 at 776. For example, physician’s knew to monitor patients receiving MTX for

gastrointestinal, hepatic, and pulmonary toxicity, as well as bone marrow suppression and stomatitis. *Id*.; *see also* Ex. 1014 at S181. And when adverse events were noted, the physician's response was to reduce the dose (in mg) or to stop therapy, not to reduce the concentration. Gershwin Decl. (Ex. 1012) at ¶ 37; *see also* PDR (Ex. 1007) at 764 ("Once optimal clinical response has been achieved, the dosage schedule should be reduced to the lowest possible amount of drug and to the longest possible rest period."). In addition, there were well known methods for reducing any dose-related toxicity–specifically, folic acid supplementation was commonly used to reduce or eliminate potentially toxic side-effects. Gershwin Decl. (Ex. 1012) at ¶ 37; Pincus (Ex. 1014) at S-181.

Finally, if there were any toxicity concerns with respect to increasing the concentration of an MTX solution, the prior art explicitly pointed them out. For example, the PDR allegedly cautions against using high concentrations of MTX for intrathecal[4] injection only, stating "the concentration for intrathecal injection should be 1 mg to 2.5 mg/ml." Ex. 1007 at 764, middle col. Importantly, the PDR does not include any such warning about increasing the concentration of MTX for intramuscular or subcutaneous administration. Gammon Decl. (Ex. 1013) at ¶ 60.

[4] Intrathecal injection is an injection into the spinal cord or brain. Gershwin Decl. (Ex. 1012) at ¶ 77.

Hospira also includes a similar warning for intrathecal administration, but not intramuscular or subcutaneous. *See* Ex. 1009 at 1 (stating that the 100 and 25 mg/ml solutions are "not suitable for intrathecal use.").

Hence, Applicant's argument during prosecution that subcutaneous injections of highly concentrated MTX solutions would be toxic is not supported by the evidence, and does not overcome the *prima facie* case of obviousness established in the Grounds above.

B. The bioavailability of MTX after subcutaneous injection is dose–not concentration–dependent

Applicant also argued during prosecution of the '231 Patent that it would not have been obvious that the bioavailability of MTX solutions with higher concentrations would be acceptable. Ex. 1002 3/21/12 at 21, OA Response. Applicant did not explain whether the bioavailability of a highly concentrated MTX solution would be too high or too low, and moreover, the blanket assertions were not accompanied by any evidentiary support. Whether or not MTX is bioavailable is a matter of dose, not concentration. Gershwin Decl. (Ex. 1012) at ¶ 93. Indeed, Brooks (Ex. 1008) compared the bioavailability of subcutaneously and intramuscularly injected MTX, and concluded that there was no difference in bioavailability. The skilled artisan would not have been concerned that the result would be different with highly concentrated solutions, because the same dose of

MTX would be administered. Gershwin Decl. (Ex. 1012) at ¶ 94. Further, the concentration of the MTX solution would not impact the total amount of MTX available to the patient, whereas the dose of MTX administered would. Gershwin Decl. (Ex. 1012) at ¶¶ 93-94. That is, a 25 mg dose of MTX is a 25 mg dose of MTX, regardless of what concentration is administered to the patient. Gershwin Decl. (Ex. 1012) at ¶¶ 93-94. Thus, Applicant's argument that there would be bioavailability concerns when administering subcutaneous injections of highly concentrated MTX solutions is not supported by the evidence, and thus cannot be a basis for overcoming the *prima facie* case of obviousness established in the Grounds above.

C. Applicant's evidence of unexpected results is not based on a comparison of the claimed invention to the closest prior art

During prosecution of the '231 Patent, Applicant attempted to prove unexpected results by citing the results reported in the 2010 Müller-Ladner paper. Ex. 1002 at 21, 3/21/12 OA Response. This reference compared the subcutaneous administration of 0.4 ml of a 50 mg/ml concentration of MTX against the subcutaneous administration of 2.0 ml of a 10 mg/ml concentration of MTX. Ex. 1011 at 15; Gershwin Decl. (Ex. 1012) at ¶ 96. According to the Applicant, "the HC treatment (high-concentration formulation of 50 mg/ml) was better tolerated than the MC treatment (medium-concentration formulation of 10 mg/ml)," which

Applicant argued "represents the surprising technical effect which was unexpectedly observed for the high methotrexate concentration underlying the present invention." Ex. 1002 at 21, 3/21/12 OA Response. This evidence of unexpected results is, however, insufficient for at least the reason that Applicant did not compare the claimed subject matter to the closest prior art. *See*, *In re De Blauwe*, 736 F.2d 699, 705 (Fed. Cir. 1984) ("[A]n applicant relying on comparative tests to rebut a *prima facie* case of obviousness must compare his claimed invention to the closest prior art."). More specifically, Applicant previously argued that Hoekstra (Ex. 1004) used a 25 mg/ml concentration of MTX and was the "closest prior art." Ex. 1002 at 20, 22. Additionally, the claims of the '231 Patent are not limited to MTX concentrations of 50 mg/ml and higher, but also include concentrations as low as 30 mg/ml. *See e.g.* Ex. 1001 at claims 1, 2, and 4-21. Thus, to show unexpected results, Applicant should have compared a 30 mg/ml MTX solution against the 25 mg/ml concentration disclosed in the prior art. Moreover, the results in the Müller-Ladner paper do not show surprising results that can be attributed to increased concentration the volume of injected MTX significantly differs between the 50 mg/ml and 10 mg/ml injections. The 50 mg/ml injection required a volume of 0.4 mls, whereas the 10 mg/ml injection required a volume of 2 mls. *See* Müller-Ladner (Ex. 1011) at Figure 1. Müller-

Ladner concedes that "[r]easons for this preference [patient's preference for the highly concentrated MTX solution] also include a smaller volume of administered drug, which improves the comfort of injection and may represent a psychological benefit for the patient." Ex. 1011 at 21 (emphasis added); Gershwin Decl. (Ex. 1012) at ¶ 99. The improved comfort reported in Müller-Ladner is not surprising because this very result was previously predicted by Jørgensen (*i.e.*, reducing volume reduces pain associated with subcutaneous injections). Jørgensen (Ex. 1004) at 731; Gershwin Decl. (Ex. 1012) at ¶¶ 99-100. Moreover, had Applicant compared the 50 mg/ml solution in the Müller-Ladner paper to the 25 mg/ml concentration disclosed in Hoekstra, patients would have been administered approximately 0.4 ml and 1.0 ml of injection solution, respectively, both of which are at or below the recommended injection volume disclosed in Jørgensen. Gershwin Decl. (Ex. 1012) at ¶¶ 97-99. Thus, Applicant's argument in the prosecution history that the 50 mg/ml (i.e, the more concentrated) solution was unexpectedly better tolerated than the 10 mg/ml solution is scientifically flawed, at least because it does not take into account the difference in volume of fluid injected. Gershwin Decl. (Ex. 1012) at ¶¶ 97-99.

Finally, the results presented in the paper at the first paragraph of page 21, which are the results relied upon by Applicant during prosecution, are overstated.

Müller-Ladner states that "[p]hysicians' assessment of the injection site showed an absence of erythema with HC [50 mg/ml] treatment in 79.9% of patients compared to 71.1% with MC [10 mg/ml] treatment, which was statistically significant." Ex. 1011 at 21. However, Table 2 on page 20 reports the "Adverse Events" from the study and notes the incidence of erythema was zero out of 131 patient receiving the 10 mg/ml MTX solution, and one out of 131 patients receiving the 50 mg/ml MTX solution. *Id*. Moreover, Müller-Ladner acknowledged that "[i]n general, quantity and quality of adverse events did not differ between the two formulations to a relevant extent." *Id*. Thus, it is unclear how the Physicians' assessment values of 79.9 and 71.1% were generated with virtually no reports of erythema in either test group. Gershwin Decl. (Ex. 1012) at ¶ 100. For at least those reasons, Applicant's evidence of unexpected results must be disregarded.

D. Zackheim does not teach away from the claimed invention

During prosecution of the '231 Patent, Applicant argued that the teachings of Zackheim (Ex. 1010) taught away from the invention. More specifically, Applicant argued that when doses of more than 50 mg were required for treatment, Zackheim chose to maintain the known concentration of 25 mg/ml and give two, one ml injections of MTX (for a total of 50 mg), rather than increasing the concentration of the MTX solution to 50 mg/ml, *e.g*, and giving a 1 ml injection (for a total of 50 mg). Ex. 1002 at 22, 3/21/12 OA Response. However,

Zackheim's "choice" to provide patients with two, one ml injections cannot be a teaching away because it does not criticize, discredit, or otherwise discourage the solution claimed, as is required for finding that a reference teaches away. *See, e.g., Galderma Labs. v. Tolmar Inc*., 737 F.3d 731, 738 (Fed. Cir. 2013) ("A reference does not teach away … if it merely expresses a general preference for an alternative invention but does not criticize, discredit, or otherwise discourage investigation into the invention claimed."); Gershwin Decl. (Ex. 1012) at ¶ 103. Moreover, one skilled in the art would recognize that Zackheim is a report by a physician regarding administration of MTX formulations available in pharmacies, not a research report regarding how MTX could be formulated. Gershwin Decl. (Ex. 1012) at ¶ 103. As such, Zackheim cannot be viewed as teaching away from the claims of the '231 patent.

XIV. CONCLUSION

For the reasons set forth herein, Petitioner requests that *inter partes* review of these claims be instituted and claims 1-22 be found unpatentable and canceled.

Respectfully submitted,

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Certificate of Service

In accordance with 37 CFR §§ 42.6(e) and 42.105, I certify that I caused to be served a true and correct copy of the foregoing PETITION FOR INTER PARTES REVIEW OF U.S. PATENT NO. 8,664,231 by overnight courier on this 22nd day of February, 2016, on the patent owner at the correspondence address of record for the subject patent as follows:

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