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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ANTARES PHARMA, INC., LEO PHARMA A/S and LEO PHARMA INC.,

Petitioners

v.

MEDAC GESELLSCHAFT FUER KLINISCHE SPEZIALPRÄPARATE MBH

Patent Owner

Case No.: Not yet assigned
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

Petitioners Antares Pharma, Inc., Leo Pharma A/S and Leo Pharma Inc., request an *Inter Partes* Review (IPR) of claims 1-22 (collectively, the "Challenged Claims") of U.S. Patent No. 8,664,231 (Ex. 1001).

II. Grounds for Standing

Petitioners certify that the '231 Patent is available for IPR and that the Petitioners are not barred or estopped from requesting IPR challenging the claims of the '231 Patent on the grounds identified in this petition.

III. Mandatory Notices

A. Real Party-In-Interest

The real parties-in-interest are Antares Pharma, Inc., Leo Pharma, Inc., and Leo Pharma A/S. 37 C.F.R. § 42.8(b)(1).

B. Related Matters

The '231 Patent is presently the subject of a lawsuit filed on March 7, 2014, by medac Pharma, Inc. and medac Gesellschaft für klinische Spezialpräparate mbH against Petitioners in the U.S. District Court for the District of New Jersey: Case No. 1:14-cv-01498-JBS-KMW. 37 C.F.R. § 42.8(b)(2). Ex. 1016.

C. Lead and Back-Up Counsel, and Service Information

Lead counsel is Sanya Sukduang, Reg. No. 46,390, of FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, LLP, 901 New York Avenue, NW Washington, DC 20001-4413, P: 202-408-4377/F: 202-408-4400,

Sanya.Sukduang@finnegan.com. Back-up counsel is Thomas Jenkins, Reg. No. 30,830,857, also of FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, LLP, 901 New York Avenue, NW Washington, DC 20001-4413, P: 202-408-4088/F: 202-408-4400, thomas.jenkins@finnegan.com. Petitioners consent to electronic service.

IV. Payment of Fees

The required fees are submitted herewith in accordance with 37 C.F.R. §§ 42.103(a) and 42.15(a). If any additional fees are due during this proceeding, the Office is authorized to charge such fees to Deposit Account No. 06-0916.

V. Identification of Challenge

A. Overview of the '231 Patent

1. The '231 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 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.

2. The '231 Claims

Claim 1, the only independent claim in the '231 patent, recites a method for treating inflammatory autoimmune diseases in a pateint 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 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 inejction 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 botte, 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.

3. The '231 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 adminstering 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 determinination 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.* Secondary references were cited by the Examiner that allegedly taught the additional elements of the dependent claims.

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 administerd 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 treatement 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 acknowleged 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 was a "surprising technical effect which was unexpectedly observed" when compared to the higher volume, but less concetrated 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 optimaization." *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.*

B. Claim Construction of Challenged Claims

A claim subject to IPR receives the "broadest reasonable construction in light of the specification of the patent in which it appears." 37 C.F.R. § 42.100(b). Unless otherwise noted below, Petitioners accept, for purposes of IPR only, that the claim terms of the '231 patent are presumed to take on their ordinary and customary meaning that they would have to one of ordinary skill in the art.

1. "Subcutaneously"

The term "subcutaneously" means:"under the skin." Weinblatt Decl. (Ex. 1012) at ¶ 48; Ex. 1001 at 5:1-5.

2. "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.

3. "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.

4. "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.

5. "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.

C. Statement of Precise Relief Requested for Each Claim Challenged

1. Claims for Which Review Is Requested

Petitioners request 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.

2. Statutory Grounds of Challenge

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

Ground	Proposed Rejections for the '231 Patent	Exhibit No(s).
1	Claims 1, 2, 4-6, 11-13, 17, and 22 are **anticipated** under 35 U.S.C. § 102(b) by US Patent No. 6,544,504 (*Grint*).	**1003**
2	Claims 7-10, 14-16, and 19-21 are **obvious** under 35 U.S.C. § 103(a) in view of US Patent No. 6,544,504 (*Grint*) and *Insulin Admin.*	**1003 and 1015**
3	Claim 18 is **obvious** under § 103(a) in view of US Patent No. 6,544,504 (*Grint*) and *Alsufyani.*	**1003 and 1006**
4	Claims 1-5, 11, 12, 13, 17, and 22 are **obvious** under § 103(a) in view of *the PDR for Mexate® or Hospira* and *Brooks.*	**1007 or 1009 and 1008**
5	Claims 7-10, 14-16, and 19-21 are **obvious** under § 103(a) in view of *the PDR for Mexate® or Hospira, Brooks*, and *Insulin Admin.*	**1007 or 1009, 1008, and 1015**
6	Claims 1-6, 11, 12, 13, 17, and 22 are **obvious** under § 103(a) in view of *Hoekstra* and *Jørgensen.*	**1004 and 1005**
7	Claims 7-10, 14-16, and 19-21 are **obvious** under § 103(a) in view of *Hoekstra, Jørgensen,* and *Insulin Admin.*	**1004, 1005, and 1015**

Ground	Proposed Rejections for the '231 Patent	Exhibit No(s).
8	Claim 18 is **obvious** under § 103(a) in view of *Hoekstra*, *Jørgensen*, and *Alsufyani*.	**1004, 1005, and 1006**

D. Overview of the Cited 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; Weinblatt Decl. (Ex. 1012) at ¶¶ 22-26; Ex. 1014 at S179-80. MTX was approved by the FDA in 1988 as a weekly therapy for treating rheumatoid arthritis. Weinblatt Decl. (Ex. 1012) at ¶ 27, citing *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. Weinblatt Decl. (Ex. 1012) at ¶ 28; 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. Weinblatt Decl. (Ex. 1012) at ¶ 30.

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, foreign priority date of the '231 patent. *See* U.S. Patent 5,644,504 ("*Grint*"; Ex. 1003); *see also* Weinblatt Decl. (Ex. 1012) at ¶¶ 57-60. 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 ¶¶ 50-54.

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 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 for Mexate®*"); *see also* Ex. 1009 ("*Hospira*"); *see also* Gammon Decl. (Ex. 1013) at ¶ 57.

In addition, these prior art concentrated MTX solutions are themselves a basis for unpatentability of the '231 claims. Both *the PDR for Mexate®* (Ex. 1007) and *Hospira* (Ex. 1009) teach 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 for Mexate®* 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.

E. Level of 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 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. Weinblatt Decl.(Ex. 1012) at ¶ 38; Gammon Decl. (Ex. 1013) at ¶ 16.

VI. Detailed Explanation of the Challenge

A. Ground 1: U.S. Patent 6,544,504 ("*Grint*;" Ex. 1003) anticipates claims 1, 2, 4, 5, 6, 11, 12, 13, 17, and 22 under 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 the July 21, 2006, foreign 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 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. Weinblatt Decl. (Ex. 1012) at ¶ 53. *Grint* also discloses that MTX may be adminstered "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 interference with the other components of the solution. Ex. 1003 at 5:64-66; 7:54-57; Weinblatt Decl. (Ex. 1012) at ¶ 53.

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 it teaches 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. Weinblatt Decl. (Ex. 1012) at ¶¶ 55-65; 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). Granting patent protection to claims 1, 2, 4, 5, 6, 11, 12, 13, 17, and 22 of the '231 patent would exclude the public from practicing *Grint*, and thus these claims in the '231 patent should be canceled.

Even though claims 1, 2, 4, 5, 6, 11, 12, 13, 17, and 22 of the '231 patent read on *Grint's* disclosed methods, Patent Owner may 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). In two recent cases, 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 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

[1] In earlier cases, the Federal Circuit 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).

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 '231 patent claims. Weinblatt Decl. (Ex. 1012) at ¶ 60. 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 the '231 patent. *See* Weinblatt Decl. (Ex. 1012) at ¶¶ 57-60, 65. 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, 5, 6, 11, 12, 13, 17, and 22 of the '231 patent, as shown in detail below in the chart. Accordingly, these claims should be canceled as anticipated by the *Grint* under § 102(b).

1. Claim chart for Ground 1.

Claim	Exemplary Citations in *Grint* (Ex. 1003)
1pre. 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

Claim	Exemplary Citations in *Grint* (Ex. 1003)
	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* Weinblatt Decl. (Ex. 1012) at ¶ 55.
1a. 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* Weinblatt Decl. (Ex. 1012) at ¶ 56.
1b. 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

Claim	Exemplary Citations in *Grint* (Ex. 1003)
	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 vegtable oils."); *see also* Weinblatt Decl. (Ex. 1012) at ¶¶ 57-58.
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 1b.
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.
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	*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*

Claim	Exemplary Citations in *Grint* (Ex. 1003)
arthroses, or psoriasis.	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* Weinblatt Decl. (Ex. 1012) at ¶ 62.
6. The method according to claim 5, wherein the inflammatory autoimmune disease is rheumatoid arthritis.	*See*, *supra*, at claim 5.
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.
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.
13. The method according to claim 11, wherein the storage container is an injection bottle, a vial, a bag, a glass	*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.

Claim	Exemplary Citations in *Grint* (Ex. 1003)
ampoule, or a carpule.	Gammon Decl. (Ex. 1013) at ¶ 45.
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.
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* Weinblatt Decl. (Ex. 1012) at ¶ 57.

B. Ground 2: Claims 7, 8, 9, 10, 14, 15, 16, 19, 20, and 21 are rendered obvious by U.S. Patent 6,544,504 ("*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, are 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 ¶49. 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; Weinblatt Decl. (Ex. 1012) at ¶ 79. *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 specification also makes clear that it was routine in the art as of 2006 to formulate injectable drugs 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."); *see also* Gammon Decl. (Ex. 1013) at ¶¶ 50-51.

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. 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 ¶ 48. Thus, *Grint*, combined with *Insulin Admin.* teaches each and every element of claims 7, 8, 9, 10, 14, 15, 16, 19, 20, and 21, and therefore these claim should be found unpatentable under 35 U.S.C. §103(a).

1. Claim chart for Ground 2.

Claim	Exemplary Citations in *Insulin Admin.* (Ex. 1015)
7. The method according to claim 1, wherein the medicament is present in a form suitable for patient self-administration.	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-

Claim	Exemplary Citations in *Insulin Admin.* (Ex. 1015)
	injected."); *see also* Gammon Decl. (Ex. 1013) at ¶ 50.
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.
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* Claim chart at section VI.A. for claim 12, showing exemplary support in *Grint*.
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 resutants."); *see also* Gammon Decl. (Ex. 1013) at ¶¶ 51-52.
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 ¶ 51.
15. The method according to claim 14, wherein the carpule and the pen injector are provided such	Ex. 1015 at S123 ("Several pen-like devices and insulin-containing cartridges are available that deliver insulin subcutaneously through a needle. In many patients (e.g., especially those who are

Claim	Exemplary Citations in *Insulin Admin.* (Ex. 1015)
that multiple applications of single dosages can be administered.	neurologically impaired and those using multiple daily injection regimes), these devices have been demonstrated to improve accuracy of insuling administration and/or adhreence."); *see also* Gammon Decl. (Ex. 1013) at ¶ 51.
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* Claim chart at section VI.A. for claim 12, showing exemplary support in *Grint*.
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* Claim chart at section VI.A. for claim 12, showing exemplary support in *Grint*.
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 ¶ 51.
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* Claim chart at section VI.A. for claim 12, showing exemplary support in *Grint*.

C. Ground 3: Claim 18 is rendered obvious by U.S. Patent 6,544,504 ("*Grint*;" Ex. 1003) in view of *Alsufyani* (Ex. 1006).

Claim 18, which recites that the rheumatoid arthritis of claim 6 is "juvenile rheumatoid arthirits" ("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 concetrated 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. Weinblatt Decl. (Ex. 1012) at ¶ 69. 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."); Weinblatt Decl. (Ex. 1012) at ¶ 68. *Alsufyani* was published in 2004, and is § 102(b) art. Accordingly, because *Grint* teaches that concetrated 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 concetrated solutions of MTX for the treatement of jRA rendering claim 18 unpatentable under 35 U.S.C. §103(a). Weinblatt Decl. (Ex. 1012) at ¶ 69.

1. **Claim chart for Ground 3.**

Claim	Exemplary Citations in *Alsufyani* (Ex. 1006)
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*, at VI.A. describing *Grint's* teachings relative to claims 1, 5, and 6, from which claim 18 depends. 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* Weinblatt Decl. (Ex. 1012) at ¶¶ 66-69.

D. Grounds 4-5: Claims 1-22 are obvious under 35 U.S.C. § 103(a) over primary references *the PDR for Mexate®* (Ex. 1007) or *Hospira* (Ex. 1009) and *Brooks* (Ex. 1008), further in view of *Insulin Admin.* (Ex. 1015) and *Alsufyani* (Ex. 1006).

1. Discussion of the primary references.

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

Exhibit 1007 ("*the PDR for Mexate®*") comprises pages 762-764 from the 1985 edition of the Physician's Desk Reference ("PDR"), and is prior art to the '231 patent. The PDR is published annually, and compiles package inserts for FDA-approved drugs. Weinblatt Decl. (Ex. 1012) at ¶ 70; 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 for Mexate® 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.* Reconstiting 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. Reconstiting 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 for Mexate®* 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. Weinblatt Decl. (Ex. 1012) at ¶ 72; Gammon Decl. (Ex. 1013) at ¶ 57. Moreover, *the PDR for Mexate®* 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. Weinblatt Decl. (Ex. 1012) at ¶ 73. Thus, *the PDR for Mexate®* 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 predecesor, 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. Weinblatt Decl. (Ex. 1012) at ¶ 75; Gammon Decl. (Ex. 1013) at ¶¶ 63-65.

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

Neither *the PDR for Mexate® nor Hospira* expressly recite subcutaneous administration. *Brooks* (Ex. 1008) supplies this teaching. *Brooks* was published in 1990 and is prior art to the '231 patent. *Brooks* was submitted to the USPTO during prosecution of the '231 patent in an Information Disclosure Statement ("IDS"), and the Examiner indicated via a signed IDS form that he considered the reference. Ex. 1002 at 14. The Examiner did not, however, use *Brooks* as a basis for any rejection.

Brooks reports that in 1990, "the intramuscular route [of administering MTX] is a desireable choice for parenteral drug administration because of the completeness of absorpotion releative 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 administerd MTX." Ex. 1008 at 91; Weinblatt Decl. (Ex. 1012) at ¶ 79. 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; Weinblatt Decl. (Ex. 1012) at ¶ 79. Intramuscular injections are painful

and most often must be administered by physician's or staff in the hospital or physician's office. Weinblatt Decl. (Ex. 1012) at ¶ 81.

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; Weinblatt Decl. (Ex. 1012) at ¶ 80. *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); Weinblatt Decl. (Ex. 1012) at 80. In other words, *Brooks* established that subcutansously administered MTX is bioequivalent to intramuscularly administered MTX. Weinblatt Decl. (Ex. 1012) at 80. *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. Weinblatt Decl. (Ex. 1012) at ¶ 82.

2. Ground 4: Claims 1-5, 11, 12, 13, 17, and 22 of the '231 patent are obvious over *the PDR for Mexate®* (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 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 in the Declarations of Weinblatt and Gammon, *the PDR for Mexate®* 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 § VI.D.1(a-b). *Brooks* (Ex. 1008) teaches that intramuscular and subcutaneous routes of MTX administration are interchangeable. Ex. 1008 at 93; Weinblatt Decl. (Ex. 1012) at ¶ 82. The skilled artisan reading these references in 2006, would have understood that the concentrations described in *the PDR for Mexate®* and *Hospira* could be administered subcutaneously. Weinblatt Decl (Ex. 1012) at ¶ 83. Indeed, nothing in *the PDR for Mexate®*, *Hospira* or *Brooks* cautions against using highly concentrated MTX solutions subcutaneously for the treatement of inflammatory autoimmune diseases. Weinblatt Decl. (Ex. 1012) at ¶ 83; Gammon Decl. (Ex. 1013) at ¶¶ 65-66.

The skilled artisan would have been motivated to use the concentrated MTX solutions described in *the PDR for Mexate®* 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; Weinblatt Decl. (Ex. 1012) at ¶ 83. Further, it was well known prior to 2006 that subcutaneous administration was desireable because it is less painful than intramuscular administration and patients could self-administer subcutaneously in the convenience of their home. Weinblatt Decl. (Ex. 1012) at ¶ 82. Thus, the skilled artisan would have expected that admininistering the highly concentrated MTX solutions disclosed *the PDR for Mexate®* or *Hospira* subcutaneously would produce the same results as administering them intramuscularly. Weinblatt Decl. (Ex. 1012) at ¶ 83.

Claims 1, 2, 4, 5, 11, 12, 13, 17, and 22 of the '231 patent should be canceled as obvious under 35 U.S.C. § 103(a) as discussed above and in the chart below.

a. **Claim chart for Ground 4 showing exemplary citations in *the PDR for Mexate®* (Ex. 1007).**

Claim	Exemplary Citations in *the PDR for Mexate® (Ex. 1007)*
1pre. A method for the treatment of inflammatory autoimmune diseases in a patient in need thereof, comprising	*The PDR for Mexate®* teaches MTX to treat an inflammatory autoimmune disease. Ex. 1007 at 764, middle column

[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 ¶.

Claim	Exemplary Citations in *the PDR for Mexate® (Ex. 1007)*
	("Psoriasis…Directions for Use: Intramuscular or intravenous administration"); *see also* Weinblatt Decl. (Ex. 1012) at ¶ 71.
1a. subcutaneously administering to said patient a medicament comprising methotrexate	*See*, *infra* at § VI.D.2(c) claim chart for ground 4 showing exemplary citations in Brooks.
1b. in a pharmaceutically acceptable solvent at a concentration of more than 30 mg/ml.	*The PDR for Mexate*® 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* Weinblatt Decl. (Ex. 1012) at ¶ 72; *see also* Gammon Dec. (Ex. 1013) at ¶57.
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 1b.
3. The method according to claim 2, wherein the methotrexate is present at a concentration of about 50 mg/ml.	*See*, *supra*, at claim 1b.
4. The method according to claim 1, wherein the pharmaceutically acceptable solvent is selected from water, water for injection	*The PDR for Mexate*® teaches MTX in a pharmaceutically acceptable solvent that is water or sodium chloride.

Claim	Exemplary Citations in *the PDR for Mexate® (Ex. 1007)*
purposes, water comprising isotonization additives and 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 ¶ 58.
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 for Mexate*® teaches administering MTX to treat psoriasis. Ex. 1007 at 764, middle column ("Psoriasis"); *see also* Weinblatt Decl. (Ex. 1012) at ¶ 71.
11. The method according to claim 1, wherein the medicament is contained in a storage container.	*The PDR for Mexate*® 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.
12. The method according to claim 11, wherein the storage container contains a total dosage amount of 5 to 5,000 mg.	*The PDR for Mexate*® 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.
13. The method according to claim 11, wherein the storage container is an injection bottle, a vial, a bag, a glass ampoule,	*The PDR for Mexate*® teaches MTX in vial. Ex. 1007 at 764, last column ("How Supplied: Mexate…20 mg vial…50 mg vial…100 mg

Claim	Exemplary Citations in *the PDR for Mexate® (Ex. 1007)*
or a carpule.	vial…250 mg vial."); *see also* Gammon Dec. (Ex. 1013) at ¶ 57.
17. The method according to claim 4, wherein the sodium chloride solution is isotonic sodium chloride solution.	*The PDR for Mexate*® 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 ¶ 58.
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 1b.

b. **Claim chart for ground 4 showing exemplary citations in *Hospira* (Ex. 1009).**

Claim	Exemplary Citations in *the Hospira* (Ex. 1009)
1pre. 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* Weinblatt Decl. (Ex. 1012) at ¶ 75.
1a. subcutaneously administering to said patient a medicament comprising methotrexate	*See*, *infra* at § VI.D.2(c) (claim 1a).
1b. 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*

Claim	Exemplary Citations in *the Hospira* (Ex. 1009)
	Weinblatt Decl. (Ex. 1012) at ¶ 75; *see also* Gammon Dec. (Ex. 1013) at ¶ 63.
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 1b.
3. The method according to claim 2, wherein the methotrexate is present at a concentration of about 50 mg/ml.	*See, supra*, at § VI.D.2(a)(claim 3).
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.
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* Weinblatt Decl. (Ex. 1012) at ¶ 75.
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.
12. The method according to	*Hospira* teaches MTX in a storage container

Claim	Exemplary Citations in *the Hospira* (Ex. 1009)
claim 11, wherein the storage container contains a total dosage amount of 5 to 5,000 mg.	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/50mls…."); *see also* Gammon Decl. (Ex. 1013) at ¶ 63.
13. The method according to claim 11, wherein the storage container is an injection bottle, a vial, a bag, a glass ampoule, or a carpule.	*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.
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.
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 1b.

c. **Claim chart for ground 4 showing exemplary citations in *Brooks* (Ex. 1008)**

Claim	Exemplary Citations in *Brooks* (Ex. 1008)
1pre. A method for the treatment of inflammatory autoimmune diseases in a patient in need thereof, comprising	*Brooks* 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* Weinblatt Decl. (Ex. 1012) at ¶ 77.
1a. subcutaneously administering to said patient a medicament	*Brooks* teaches subcutaneous administration of MTX.

Claim	Exemplary Citations in *Brooks* (Ex. 1008)
comprising methotrexate	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* Weinblatt Decl. (Ex. 1012) at ¶ 79.
1b. in a pharmaceutically acceptable solvent at a concentration of more than 30 mg/ml.	*See*, *supra* at § VI.D.2(a-b) (claim 1b).
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 § VI.D.2(a-b) (claim 2).
3. The method according to claim 2, wherein the methotrexate is present at a concentration of about 50 mg/ml.	*See*, *supra* at § VI.D.2(a-b) (claim 3).
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.	*See*, *supra* at § VI.D.2(a-b) (claim 4).
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,	*See*, *supra* at § VI.D.2(a-b) (claim 5).

Claim	Exemplary Citations in *Brooks* (Ex. 1008)
bronchial asthma, Alzheimer's disease, multiple sclerosis, Bechterew's disease, joint arthroses, or psoriasis.	
6. The method according to claim 5, wherein the inflammatory autoimmune disease is rheumatoid arthritis.	*See*, *supra* at claim 1pre.
11. The method according to claim 1, wherein the medicament is contained in a storage container.	*See*, *supra* at § VI.D.2(a-b) (claim 11).
12. The method according to claim 11, wherein the storage container contains a total dosage amount of 5 to 5,000 mg.	*See*, *supra* at § VI.D.2(a-b) (claim 12).
13. The method according to claim 11, wherein the storage container is an injection bottle, a vial, a bag, a glass ampoule, or a carpule.	*See*, *supra* at § VI.D.2(a-b) (claim 13).
17. The method according to claim 4, wherein the sodium chloride solution is isotonic sodium chloride solution.	*See*, *supra* at § VI.D.2(a-b) (claim 17).
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 § VI.D.2(a-b) (claim 22).

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

As discussed above, primary references *the PDR for Mexate®* or *Hospira* and *Brooks* teach methods for treating inflammatory autoimmune diseases via subcutaneous injections of MTX at concentrations greater than 30 mg/ml. *See* §

VI.D.2, *supra*. These primary references do notexpressly disclose MTX packaged in forms suitable for self-administration, ready-made syringes, or injection devices such as pen-injectors. But as discussed above in § VI.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 expecation of success, to 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 reinfirced 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 ¶ 54. Thus, the combination of *the PDR for Mexate®* 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 §§ VI.B and D detailing the exemplary citations in *the PDR for Mexate®*, *Hospira*, *Brooks*, and *Insulin Admin.*, respectivley, for each and every element of claims 7-10, 14-16, and 19-21.

E. Grounds 6-8: Claims 1-22 are rendered obvious by primary references *Hoekstra* (Ex. 1004) and *Jørgensen* (Ex. 1005), further in view of *Insulin Admin.* (Ex. 1015) and secondary reference *Alsufyani* (Ex. 1006).

1. Discussion of the Primary References

a. The primary reference *Hoekstra* (Ex. 1004) teaches subcutaneous administration of MTX at high doses.

Exhibit 1004 ("*Hoekstra*") teaches that high doses of MTX (up to 40 mg) can be successfully administered to RA patients via the subcutaneous route. Weinblatt Decl. (Ex. 1012) at ¶ 86. *Hoekstra* was published in 2004, and thus is prior art to the '231 patent. *Hoekstra* was considered by the Examiner during prosecution of the '231 patent, and was cited as a basis for the Examiner's rejection of the claims under 35 U.S.C. § 103(a). Ex. 1002 at 7, 12/21/11 OA.

During prosecution of the '231 patent, Applicant conceded that *Hoekstra* "clearly represents the closest prior art," and represented that it "disclose[s] methotrexate solutions to be administered subcutaneously for treating inflammatory autoimmune diseases with a concentration of 25 mg/ml." Ex. 1002 at 20, 22, 3/21/12 OA Response. Applicant also conceded that *Hoekstra* taught absolute doses (in mg) of methotrexate between 25 and 40 mg per week. *Id.* at 10. Although *Hoekstra* does not disclose concentrations of MTX greater than 25 mg/ml, *Jørgensen* (Ex. 1005) provides a motivation to use more concentrated formulations of MTX as explained below.

b. The primary reference *Jørgensen* (Ex. 1005) teaches that the volume of subcutaneously injected solutions

should be formulated to contain less than one milliliter (mL).

Jørgensen teaches that subcutaneously injected solutions should be formulated in volumes less than one milliliter (mL) because such volumes reduce the pain associated with the injection and increase patient comfort and compliance. Ex. 1005 at 731; Weinblatt Decl. (Ex. 1012) at ¶ 89. *Jørgensen* was published in 1996 and is prior art to the '231 patent. *Jørgensen* was not provided to the USPTO during prosecution of the '231 patent, despite the fact that Applicant knew of *Jørgensen* and its materiality during prosecution of the '231 patent. *See* Certified English Translation of Portion of EPO prosecution for EP Applicaton No. 07786239.9 (Ex. 1017) at 36 ("[*Jørgensen*] is prima facie relevant for the assessment of inventive activity").

Jørgensen reports a clinical trial comparing the pain associated with subcutaneous administrations of four different volumes of injected solution. Ex. 1005 at 731. *Jørgensen* found that the pain associated with subcutaneous injection is directly related to the volume of injected solution. More specifically, *Jørgensen* concluded that "[t]he pain of subcutaneous injection is related to injection volume," and that "pain is significantly increased at an injection volume greater than or equal to 1.0 mL." Ex. 1005 at 729; 731. According to *Jørgensen,* "[i]n order to optimize patient convenience in relation to subcutaneous administration, the results from this study should be considered in relation to the formulation of injection fluids." *Id. Jørgensen* concludes

that subcutaneously injected solutions should be provided in "less than one mL." *Id.* at 731.

2. Ground 6: Claims 1-6, 11, 12, 13, 17, and 22 are rendered obvious by *Hoekstra* (Ex. 1004) and *Jørgensen* (Ex. 1005).

Hoekstra (Ex. 1004) teaches that high doses of MTX (up to 40 mg) can be successfully administered to RA patients via subcutaneous injections. *Jørgensen* explains that patients sometimes complain about pain associated with subcutaneous injections. Ex. 1005 at col. 729-30. To address the pain associated with subcutaneous injections, *Jørgensen* teaches that the doses should be formulated in volumes less than one mL. To subcutaneously administer the high MTX dose disclosed in *Hoekstra* in less than one mL as taught by *Jørgensen* would require either: 1) increasing the *concentration* and administering less than one mL; or 2) keeping the concentration the same and splitting this dose between two separate injections, each having less than one mL (as discussed in *Zackheim* (Ex. 1010)). Weinblatt Decl. (Ex. 1012) at ¶ 90; Gammon Decl. (Ex. 1013) at ¶ 72.

Here, the person of ordinary skill in the art had good reason, reducing pain, to pursue the available options for reducing the volume of subcutaneously injected MTX solutions according to *Jørgensen*, in order to administer the high (40 mg) MTX doses disclosed in *Hoekstra*. The available options were finite–indeed, there were only two. Moreover, there was no technical impediment preventing a skilled artisan from formulating the 40 mg dose of MTX for subcutaneous administration, disclosed in

Hoekstra so that the injectable volume was less than 1 mL (i.e., a concentration greater than 40 mg/ml). Gammon Decl. (Ex. 1013) at ¶ 73. And the success of both options were predictable–whether or not MTX is successful in treating an inflammatory autoimmune disease is dependent on the dose of MTX, not on the concentration. Weinblatt Decl. (Ex. 1012) at ¶¶ 100-01; *see also* §VI.F(1-2), *infra*. Therefore the claimed methods are not the product of innovation but of ordinary skill and common sense. *See KSR*, 550 U.S. at 402-3 (2007) ("When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense."); Weinblatt Decl. (Ex. 1012) at ¶ 90. As such, claims 1-6, 11, 12, 13, 17, and 22 should be cancelled as unpatentable under 35 U.S.C. §103(a).

a. Claim chart for Ground 6 showing exemplary citations in *Hoekstra* (Ex. 1004) and *Jørgensen* (Ex. 1007).

Claim	Exemplary Citations in *Hoekstra* (Ex. 1004) *and Jørgensen* (Ex. 1007)
1pre. A method for the treatment of inflammatory autoimmune diseases in a patient in need thereof, comprising	*Hoekstra* teaches MTX to treat rheumatoid arthritis. Ex. 1004 at 645 ("Methotrexate (MTX) is commonly used in weekly single dose regimens in the treatment of rheumatoid arthritis."); *see also* Weinblatt Decl. (Ex. 1012) at ¶ 85.
1a. subcutaneously administering	*Hoekstra* teaches administering MTX

Claim	Exemplary Citations in *Hoekstra* (Ex. 1004) *and Jørgensen* (Ex. 1007)
to said patient a medicament comprising methotrexate	subcutaneously to treat rheumatoid arthritis. Ex. 1004 at 646 ("we performed a crossover pharmacokinetic study in adult patients with RA, comparing the bioavailability of oral and subcutaneous MTX at doses ≥ 25 mg weekly."); *see also* Weinblatt Decl. (Ex. 1012) at ¶ 86.
1b. in a pharmaceutically acceptable solvent at a concentration of more than 30 mg/ml.	*Hoekstra* teaches providing doses of MTX as high as 40 mg. *Jørgensen* teaches reducing the volume of subcutaneously injected solutions, thus providing reason to increase the concentration of *Hoekstra's* high dose MTX. *Hoekstra* (Ex. 1004) at 647 ("Our data suggest that doses between 25 and 40 mg MTX per week, admistered orally, result in limited bioavailability. Bioavailability is enhanced by the subctutaneous route of administration…."); *see also* *Jørgensen* (Ex. 1007) at 731("The pain of subcutaneous injection is related to the injection volume….In order to optimize patient convenience in relation to subcutaneous administration, the results from this study should be considered In relation to the formulation of injection fluids. The volume should generally be less than 1.0 mL…."); *see also* Weinblatt Decl. (Ex. 1012) at ¶ 86.
2. The method according to claim 1, wherein the methotrexate is present at a concentration of	*See*, *supra*, at claim 1b.

Claim	Exemplary Citations in *Hoekstra* (Ex. 1004) *and Jørgensen* (Ex. 1007)
more than 30 mg/ml to 100 mg/ml.	
3. The method according to claim 2, wherein the methotrexate is present at a concentration of about 50 mg/ml.	*See*, *supra*, at claim 1b.
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.	*Hoekstra's* MTX solution was administered to human patients, and therefore was present in a pharmaceutically acceptable solvent. Gammon Decl. (Ex. 1013) at ¶ 69.
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.	*Hoekstra* teaches subcutaneous administration of MTX to treat rheumatoid arthritis. Ex. 1004 at 645 ("Methotrexate (MTX) is commonly used in weekly single dose regimens in the treatment of rheumatoid arthritis."); *see also* Weinblatt Decl. (Ex. 1012) at ¶ 85.
6. The method according to claim 5, wherein the inflammatory autoimmune disease is rheumatoid arthritis.	*See*, *supra*, at claim 5.
11. The method according to claim 1, wherein the medicament is contained in a storage container.	*Hoekstra* teaches an injectable solution of MTX which is necessarily stored in a container. Gammon Decl. (Ex. 1013) at ¶ 69.
12. The method according to claim 11, wherein the storage container contains a total dosage amount of 5 to 5,000 mg.	*See*, *supra*, at claim 1b.
13. The method according to	*Hoekstra* teaches an injectable solution of

Claim	Exemplary Citations in *Hoekstra* (Ex. 1004) *and Jørgensen* (Ex. 1007)
claim 11, wherein the storage container is an injection bottle, a vial, a bag, a glass ampoule, or a carpule.	MTX which must be stored in a container, including an injection bottle, a vial, a bag, a glass ampoule, or a carpule. Gammon Decl. (Ex. 1013) at ¶ 69.
17. The method according to claim 4, wherein the sodium chloride solution is isotonic sodium chloride solution.	*Hoekstra* teaches an injectable solution of MTX for administration to patients, which is commonly an isotonic sodium chloride solution. Gammon Decl. (Ex. 1013) at ¶ 69.
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 1b.

3. Ground 7: Claims 7-10, 14-16, and 19-21 are rendered obvious by *Hoekstra* (Ex. 1004) and *Jørgensen*, in view of *Insulin Admin.* (Ex. 1015).

As discussed above, primary reference *Hoekstra* and *Jørgensen* teach methods for treating inflammatory autoimmune diseases via subcutaneous injections of MTX at concentrations greater than 30 mg/ml. *See* § VI.E.1-2, *supra*. These primary references do not, however, explicitly disclose MTX packaged in forms suitable for self-administration, ready-made syringes, or injection devices such as pen-injectors. As discussed above, *Insulin Admin.* (Ex. 1015) discloses that such injection devices were available for delivering injectable medicaments. *See* § VI.B, *supra*; Ex. 1015 at S123-24; Gammon Decl. (Ex. 1013) at ¶ 50-51. Thus, one of ordinary skill in the art would be motivated, with a reasonable expecation of success, to package a 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. This Ground is further reinfirced 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 ¶ 53. Accordingly, the combination of *Hoekstra*, *Jørgensen*, and *Insulin Admin.* teaches each and every element of claims 7-10, 14-16, and 19-21, and therefore these claim should be found unpatentable under 35 U.S.C. §103(a).

The Board is referred above to §§VI.B and VI.E.1-2 detailing the exemplary citations in the art supporting this Ground and the cancellation of claims 7-10, 14-16, and 19-21 as obvious under 35 U.S.C. § 103(a).

4. Ground 8: Claim 18 is rendered obvious by *Hoekstra* (Ex. 1004) and *Jørgensen* (Ex. 1005), in view of secondary reference *Alsufyani* (Ex. 1006).

As discussed above, primary references *Hoekstra* and *Jørgensen* teach methods for treating inflammatory autoimmune diseases via subcutaneous injections of MTX at concentrations greater than 30 mg/ml. *See* § VI.E.1-2, *supra*. These primary references do not, however, explicitly disclose juvenile rheumatoid arthritis. *Alsufyani* makes up for this deficiency by teaching that subcutaneously delivered methotrexate is an effective therapy for juvenille arthritis patients. Ex. 1006 at 179, Abstract; *see also*, § VI.C, *supra*. More specifically, because *Hoekstra* and *Jørgensen* teach methods for treating rheumatoid arthritis via subcutaneous injections of MTX at concentrations greater than 30 mg/ml, one of ordinary skill in the art would be motivated, with a

reasonable expectation of success, to treat jRA with the highly concentrated MTX solutions taught by *Hoekstra* and *Jørgensen* based on *Alsufyani's* disclosure that MTX is useful for treating jRA. Weinblatt Decl. (Ex. 1012) at ¶ 92. The Board is referred to §§ VI.C and VI.E.1-2 detailing the exemplary citations in *Hoesktra*, *Jørgensen*,and *Alsufyani* for each and every element of claim 18. Thus, claim 18 should be canceled as obvious under 35 U.S.C. § 103(a).

F. 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.

1. Any toxicity associated with MTX after subcutaneous injection is dose, not concentration dependent.

Applicant argued during prosection 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. Weinblatt Decl. (Ex. 1012) at ¶ 34. For example, *the PDR for Mexate®* cautions that *doses* of "50 mg per week should ordinarily not be exceeded," and that "Mexate has a high potential for serious toxicity which is usually *dose-related*." Ex. 1007 at 763(emphasis added). *Hospira* states similar cautions. 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 toxivity. For example, *Weinblatt*

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

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–not concentration– dependent. Weinblatt Decl. (Ex. 1012) at ¶ 94, 99.

Additionally, *the PDR for Mexate®* 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"; Weinblatt Decl. (Ex. 1012) at ¶ 83. 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; Weinblatt Decl. (Ex. 1012) at ¶ 81-83. Indeed, *Brooks* expressed no concern, warning, or belief that the concentration of MTX would alter his conclusion that subcutaneous and intermuscular 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 for Mexate®* and *Hospira* could be administered subcutaneously without raising issues of toxicity or bioavailability. Weinblatt Decl.(Ex. 1012) at IX.A and IX.B.

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 antirheumatid 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. 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; Weinblatt Decl. (Ex. 1012) at ¶ 25. 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 ¶ 36; 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. Weinblatt Decl. (Ex. 1012) at ¶ 36; *see also the PDR for Mexate®* (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. Weinblatt Decl. (Ex. 1012) at ¶ 36; *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 *the PDR for Mexate* 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 for Mexate* does not include any such warning about increasing the concentration of MTX for intramuscular administration. Gammon Decl. (Ex. 1013) at ¶ 60. *Hospira* also includes a similar warning for intrathecal administration, but not intramuscular. *See* Ex. 1009 at 1 (stating that the 100 and 25 mg/ml solutions are "not suitable for intrathecal use.").

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.

2. 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

[44] Intrathecal injection is an injection into the spinal cord or brain. Weinblatt Decl. (Ex. 1012) at ¶ 26.

concentrations would be acceptable. Ex. 1002 3/21/12 at 21, OA Response. Applicant did not explain whether the bioavialbility 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. Weinblatt Decl. (Ex. 1012) at ¶ 100. 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. Weinblatt Decl. (Ex. 1012) at ¶ 100. 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. Weinblatt Decl. (Ex. 1012) at ¶ 100. That is, a 25 mg dose of MTX is a 25 mg dose of MTX, regardless of what concentration is administered to the patient. Weinblatt Decl. (Ex. 1012) at ¶ 100. 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.

3. 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 concetration of MTX. Ex. 1011 at 15; Weinblatt Decl. (Ex. 1012) at ¶ 103. 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 suprising technical effect which was unexpectedly observed for the high methotrexate concetration 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 argued that *Hoekstra* (Ex. 1004) used a 25 mg/ml concetration 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 concetrations 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 concetration disclosed in the prior art. Moreover, the results in the *Müller-Ladner* paper do not show surprising results that can be attributed to increased conentration 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 Figue 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; Weinblatt Decl. (Ex. 1012) at ¶ 106. The improved comfort reported in *Müller-Ladner* is not suprising because this very result was previously predicted by *Jørgensen* (i.e., reducing volume reduces pain associated wth subcutaneous injections) *Jørgensen* (Ex. 1004) at 731; Weinblatt Decl. (Ex. 1012) at ¶ 106. 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*. Weinblatt Decl. (Ex. 1012) at ¶ 89. Thus, Applicant's argument in the prosecution history that the 50 mg/ml (i.e, the more concentrated) solution was unexpectdly better tolerated than the 10 mg/ml solution is

scientifically flawed because it does not take into account the difference in volume of fluid injected. Weinblatt Decl. (Ex. 1012) at ¶ 103.

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 "Physicians' 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 pateint 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. Weinblatt Decl. (Ex. 1012) at ¶ 107. Thus, Applicant's evidence of unexpected results must be disregarded as they do not present an actual difference in result that was unexpected.

4. *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 specificially, 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. *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."); Weinblatt (Ex. 1012) at ¶ 110. Moreover, one skilled in the art would recognize that *Zackheim* is a report by a physician regarding administration of MTX formulations avaiable in pharmacies, not a research report regarding how MTX could be formulated. Weinblatt Decl. (Ex. 1012) at ¶ 109-10. As such, *Zackheim* cannot be viewed as teaching away from the claims of the '231 patent.

VII. Conclusion

Thus, Petitioners respectfully request *inter partes* review of claims 1-22 of U.S. Patent No. 8,664,231.

Respectfully submitted, July 1, 2014

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§ 42.6(e) and 42.105(a), I, John W. Kozikowski, certify that on this 1st day of July, 2014, a copy of

PETITION FOR INTER PARTES REVIEW

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