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Paper 54
Entered: February 7, 2018

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

KOIOS PHARMACEUTICALS LLC,
Petitioner,

v.

MEDAC GESELLSCHAFT FÜR KLINISCHE SPEZIALPRÄPARATE MBH,
Patent Owner.

Case IPR2016-01370
Patent 8,664,231 B2

Before JACQUELINE WRIGHT BONILLA, *Vice Chief Administrative Patent Judge*, TONI R. SCHEINER, and ERICA A. FRANKLIN, *Administrative Patent Judges*.

SCHEINER, *Administrative Patent Judge*.

FINAL WRITTEN DECISION
35 U.S.C. § 318(a) and 37 C.F.R. § 42.73

I. INTRODUCTION

Koios Pharmaceuticals LLC ("Petitioner") filed a Petition on July 20, 2016, requesting an *inter partes* review of claims 1–22 of U.S. Patent No. 8,664,231 B2 (Ex. 1001, "the '231 patent"). Paper 1 ("Pet."). Petitioner provided the Declarations of Donald R. Miller, Pharm.D (Ex. 1033), and Michael H. Schiff, M.D. (Ex. 1034), in support of its positions. medac Gesellschaft für klinische Spezialpräparate mbH ("Patent Owner") filed a Preliminary Response on November 10, 2016. Paper 11 ("Prelim. Resp.").

We instituted *inter partes* review on February 8, 2017 as to claims 1–22. Paper 13 ("Institution Decision" or "Inst. Dec."). Specifically, we instituted *inter partes* review on the following grounds:

Reference(s)	**Basis**	**Claim(s)**
Grint[1]	§ 102(b)[2]	1, 2, 4–6, 11–13, 17, and 22
Grint, Arthur,[3] Moitra,[4] and Insulin Admin.[5]	§ 103(a)	7–10, 14–16, and 19–21

[1] U.S. Patent No. 6,544,504 B1, issued April 8, 2003 (Ex. 1003, "Grint").

[2] The Leahy-Smith America Invents Act, Pub. L. No. 112-29, 125 Stat. 284 (2011) ("AIA"), amended 35 U.S.C. §§ 102 and 103. Because the '231 patent has an effective filing date before March 16, 2013, we refer to the pre-AIA versions of 35 U.S.C. §§ 102 and 103.

[3] Valerie Arthur et al., *A Study of Parenteral Use of Methotrexate in Rheumatic Conditions*, 11 J. CLINICAL NURSING 256 (2002) (Ex. 1023, "Arthur").

[4] R.K. Moitra et al., *Caveats to the Use of Parenteral Methotrexate in the Treatment of Rheumatic Disease*, 44 RHEUMATOLOGY 256 (2005) (Ex. 1025, "Moitra").

[5] Am. Diabetes Ass'n, *Insulin Administration*, 26 DIABETES CARE S121 (Supp. 1 2003) (Ex. 1015, "Insulin Admin.").

Reference(s)	**Basis**	**Claim(s)**
Grint and Alsufyani[6]	§ 103(a)	18
Wyeth[7]	§ 102(b)	1–6, 11–13, 17, 18, and 22
Wyeth, Brooks,[8] Arthur, and Moitra	§ 103(a)	1–6, 11–13, 17, 18, and 22

Inst. Dec. 37.

Patent Owner filed a Patent Owner Response (Paper 24, "PO Resp."), and provided the Declarations of Elena M. Massarotti, M.D. (Ex. 2018), Sean Nicholson, Ph.D. (Ex. 2032), Thomas M. Zizic, M.D. (Ex. 2092), and John S. Clark, Pharm.D. (Ex. 2093) in support of its positions. Petitioner filed a Reply (Paper 37, "Reply"), and Patent Owner filed a Surreply (Paper 43, "Surreply"). We granted Patent Owner's request to file the Surreply to allow Patent Owner to cite to additional portions of Dr. Zizic's deposition testimony intended to provide the full context of portions of Dr. Zizic's deposition testimony cited by Petitioner in the Reply. Paper 42, 2–3.

Additionally, Patent Owner filed a Motion to Exclude Evidence (Paper 39, "Motion to Exclude" or "Mot. to Exclude"), Petitioner filed a

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[6] Khayriah Alsufyani et al., *The Role of Subcutaneous Administration of Methotrexate in Children with Juvenile Idiopathic Arthritis Who Have Failed Oral Methotrexate*, 31 J. RHEUMATOLOGY 179 (2004) (Ex. 1006, "Alsufyani").

[7] Wyeth Pharmaceuticals, Methotrexate Sodium for Injection (2004) (Ex. 1021, "Wyeth").

[8] Paul J. Brooks et al., *Pharmacokinetics of Methotrexate Administered by Intramuscular and Subcutaneous Injections in Patients with Rheumatoid Arthritis*, 33 ARTHRITIS & RHEUMATISM 91 (1990) (Ex. 1008, "Brooks").

Response to the Motion to Exclude (Paper 46), and Patent Owner filed a Reply in support of the Motion to Exclude (Paper 49).

We heard oral argument on November 7, 2017. A transcript of the argument has been entered into the record. Paper 53 ("Tr.").

We have jurisdiction under 35 U.S.C. § 6. This Final Written Decision is issued pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73. To prevail, Petitioner must establish facts supporting its challenge by a preponderance of the evidence. *See* 35 U.S.C. § 316(e); 37 C.F.R. § 42.1(d). For the reasons that follow, we determine that Petitioner has not proven by a preponderance of the evidence that claims 1–22 are unpatentable. Patent Owner's Motion to Exclude Evidence is dismissed as moot.

A. Related Proceedings

Petitioner and Patent Owner identify a district court action involving the '231 patent, titled *medac Pharma, Inc. v. Antares Pharma, Inc.*, No. 1:14-cv-1498-JBS-KMW (D.N.J.). Pet. 2; Paper 4, 2. The parties also identify two prior proceedings at the Board, IPR2014-01091 ("the -1091 IPR") and IPR2016-00649 ("the -649 IPR"), as well as Decisions on Institution in each of those cases, addressing challenges of the same patent and claims at issue here. Pet. 2–3; Paper 12, 3; *Frontier Therapeutics, LLC v. medac Gesellschaft für klinische Spezialpräparate mbH*, Case IPR2016-00649 (PTAB Sept. 1, 2016) (Paper 10); *Antares Pharma, Inc. v. medac Gesellschaft für klinische Spezialpräparate mbH*, Case IPR2014-01091 (PTAB Jan. 6, 2015) (Paper 7). The district court litigation settled in April 2015. Paper 4, 2. The -1091 IPR and -649 IPR proceedings were terminated in view of settlements in April 2015 and December 2016, respectively. Pet. 3; Paper 12, 3.

Patent Owner also identifies U.S. Patent Application Serial No. 14/635,542 ("the '542 application"), filed March 2, 2015 (now abandoned). Paper 4, 2.

B. The '231 Patent

The '231 patent relates to a method for treating inflammatory autoimmune diseases, such as rheumatoid arthritis, juvenile arthritis, and psoriasis, by subcutaneously administering a concentrated methotrexate solution comprising more than 30 mg/ml of methotrexate. Ex. 1001, Abstract, 3:59–67, 8:43–47. Methotrexate is a cytostatic agent that has been known since the early 1950s in the field of oncology, particularly for treating leukemia in children and breast cancer. *Id*. at 1:14–17, 1:24–27. Methotrexate also was used to treat psoriasis, and first observed in the late 1950s as a treatment for individual rheumatoid arthritis cases. *Id.* at 1:28–32.

According to the '231 patent, "[o]ver the years, methotrexate has become the gold standard in the treatment of rheumatoid arthritis." *Id*. at 2:34–36. As a basic therapeutic for rheumatoid arthritis, methotrexate is administered orally or parenterally, once a week, over a long period of time, sometimes throughout the patient's lifetime. *Id*. at 2:37–41. Methotrexate is dosed significantly lower in the treatment of rheumatoid arthritis than in the treatment of tumors, sometimes up to 1,000 times lower. *Id.* at 1:56–59. Anti-rheumatic therapy is therefore referred to as "low-dosage methotrexate therapy." *Id.* at 1:59–60. In this capacity, methotrexate is administered only once per week, in dosages ranging from 5–30 mg per week in Germany, and up to 40 mg per week in other European countries. *Id.* at 1:60–65.

The ’231 patent discloses a ready-made syringe and carpule containing a methotrexate solution, as well as a pen-injector comprising the ready-made syringe and/or carpule. *Id*. at 1:5–13. The ’231 patent states that ready-made syringes containing methotrexate for the treatment of rheumatoid arthritis are known from the prior art, where the active substance is present at a concentration of up to 25 mg/ml in a pharmaceutically acceptable solvent. *Id*. at 2:26–31. The ’231 patent, however, further states that “subcutaneous administration in particular has its difficulties . . . due to the problem of having to inject the required relatively large amount of active substance solution (e.g. up to 3 ml . . .) under the skin every week, which was especially difficult to convey to children.” *Id*. at 2:44–51. In other words, the ’231 patent recognizes that although the prior art ready-made syringes have had a positive impact on patient compliance (i.e., the degree of treatment acceptance on the part of the patient), injecting large amounts of liquid under the skin leads to reduced patient compliance. *Id.* at 4:14–16, 4:65–5:13.

According to the ’231 patent, a need therefore exists for a methotrexate solution that can be administered to patients, including children, as easily and painlessly as possible, to provide a high degree of patient compliance. *Id*. at 2:53–58. The ’231 patent seeks to address this need by providing methotrexate formulations in higher concentrations than those known in the prior art, which in turn allows for a smaller liquid volume for injection. *Id.* at 3:16–27, 5:5–23. The ’231 patent states that the smaller volumes of liquid are easier to convey to patients, particularly children, and can be expected to have a further positive impact on patient compliance. *Id.* at 5:5–23.

C. Illustrative Claim

Claim 1 of the '231 patent, the only independent claim, is illustrative and is reproduced below:

> 1. A method for the treatment of inflammatory autoimmune diseases in a patient in need thereof, comprising subcutaneously administering to said patient a medicament comprising methotrexate in a pharmaceutically acceptable solvent at a concentration of more than 30 mg/ml.

Id. at 8:43–47. Dependent claims 2–22 recite additional limitations regarding methotrexate concentrations and dosages; the types of solvent used; the types of inflammatory autoimmune diseases treated; suitability for self-administration; the medicament being contained in an injection device (such as a ready-made syringe or a pen injector) and in a storage container (such as a carpule); and administering single and multiple applications. *Id.* at 8:48–10:20.

II. ANALYSIS

A. Level of Ordinary Skill in the Art

Petitioner asserts that "[t]he cited art demonstrates the level of skill in the art," and

> [f]urther, a person of ordinary skill in the art would have either a Pharm.D. or Ph.D. in pharmaceutical sciences, pharmacology, or a related discipline; an M.D. or D.O. with experience in using oral and injectable [methotrexate] to treat inflammatory autoimmune diseases; or a person with a lesser degree with several years of experience in formulating and/or administering methotrexate for injection, such as a nurse or pharmacy technician.

Pet. 11. Patent Owner provides a similar description of a person having ordinary skill in the art. PO Resp. 15. In comparison with Petitioner's description, Patent Owner's description limits the Pharm.D. and Ph.D.

degrees to the fields of pharmacology, pharmaceutics, and chemistry; does not refer to a D.O.; and allows for a person with a lesser degree to have several years of experience only in the context of "methotrexate preparation." *See id.* Accordingly, because Petitioner's description encompasses a wider range of individuals having ordinary skill in the art, and such a description is supported by the record as a whole, we adopt Petitioner's description of the level of ordinary skill in the art, but we note that our disposition of this case would not differ under either Petitioner's or Patent Owner's description.

B. Claim Construction

In an *inter partes* review, claim terms in an unexpired patent are interpreted according to their broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144–46 (2016). Under that standard, claim terms generally are given their ordinary and customary meaning, as would be understood by one of ordinary skill in the art in the context of the entire disclosure. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). Only terms which are in controversy need to be construed and only to the extent necessary to resolve the controversy. *See Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011); *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999).

We determine that only the claim term "subcutaneously," which appears in independent claim 1 ("subcutaneously administering . . . a medicament"), requires discussion for resolution of the controversy in this case. In the Petition, Petitioner asserted that "subcutaneously" means

"[u]nder the skin." Pet.10. In the Preliminary Response, Patent Owner argued that subcutaneous administration is distinct from, and does not include, intramuscular or intravenous administration, despite the fact that all three involve administration at some location under the skin. Prelim. Resp. 20–21.

In the Institution Decision, we agreed with Patent Owner that the broadest reasonable construction of "subcutaneously" in light of the specification denotes a route of administration that is distinct from intramuscular (in a muscle) or intravenous (in a vein). Inst. Dec. 12–13. We noted that the specification of the '231 patent expressly uses those three terms separately, indicating that they have different meanings. Ex. 1001, 4:4–6 ("The medicaments of the present invention are administered . . . by intravenous, intramuscular or subcutaneous injection."); *id.* at 5:32–35.

Neither Petitioner nor Patent Owner disputes our preliminary determination. PO Resp. 14–15. Having reviewed our interpretation in light of the full record developed at trial, we maintain our determination that "subcutaneously" means administration under the skin, but does not include intramuscular or intravenous administration.

C. Anticipation by Grint

Petitioner asserts that Grint anticipates claims 1, 2, 4–6, 11–13, 17, and 22 of the '231 patent under 35 U.S.C. § 102(b). Pet. 12–22. Patent Owner argues that Petitioner has failed to prove by a preponderance of the evidence that Grint discloses both "subcutaneous administration" and a medicament comprising methotrexate at a "concentration of more than 30 mg/ml" (PO Resp. 18), "much less those elements as 'arranged as in the claim[s]'" (*id.*).

1. Grint

Grint describes treating autoimmune diseases, such as rheumatoid arthritis and psoriasis, by administering a combination of interleukin 10 and methotrexate. Ex. 1003, 2:23–35. Grint states that it was unexpectedly discovered that a combined/concurrent administration of interleukin 10 and methotrexate causes synergistic and unexpectedly strong benefits. *Id.* at 2:44–51. The interleukin 10 and methotrexate may be administered either together in a single pharmaceutical composition or separately. *Id.* at 3:20–21.

Grint states that methotrexate "may be administered in a manner as is conventionally practiced," citing to Goodman.[9] *Id.* at 5:20–23 (citing Ex. 2019, 1266[10]). Grint specifically identifies parenteral, intraperitoneal, and intravenous administration of methotrexate. *Id.* at 5:64–65, 7:5. Grint further teaches that the methotrexate is compounded "for convenient and effective administration in effective amounts" ranging from about 0.1 to 400 mg (preferably from 1 to 35 mg and most preferably from 10 to 25 mg), in proportions ranging from about 0.1 to about 40 mg/ml in a pharmaceutically acceptable carrier. *Id.* at 6:60–7:1.

Example 1 of Grint presents a study evaluating the safety and tolerability of administering a combination of interleukin-10 and methotrexate to patients with active rheumatoid arthritis. *Id.* at 7:40–48,

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[9] Paul Calabresi & Robert E. Parks, Jr., *Antiproliferative Agents and Drugs Used for Immunosuppression*, *in* GOODMAN AND GILMAN'S THE PHARMACOLOGICAL BASIS OF THERAPEUTICS 1247, 1266 (7th ed. 1985) (Ex. 2019, "Goodman").

[10] Grint appears to contain a typographical error in citing to page 1299 of Goodman, as opposed to page 1266. *Compare* Ex. 2019, 1266 (discussing methotrexate) *with id.* at 1299 (discussing cyclosporine).

7:66–8:2. In that study, Grint indicates that doses of methotrexate in the amount of 12.5–25 mg/week were given to the patients by oral, subcutaneous, or intramuscular administration. *Id.* at 7:56–57, 8:1–2.

2. Analysis

Claim 1 recites "subcutaneously administering . . . a medicament comprising methotrexate . . . at a concentration of more than 30 mg/ml" to a patient in need of treatment for an inflammatory autoimmune disease. Ex. 1001, 8:44–47. In contending that Grint anticipates this claim, Petitioner relies on Grint's statement that "methotrexate is generally present in from about 0.1 to about 40 mg/ml of carrier," together with Grint's Example 1, which describes a study in which a 12.5–25 mg/week dose of methotrexate was given to rheumatoid arthritis patients by oral, subcutaneous, or intramuscular administration. Pet. 13–14 (citing Ex. 1003, 6:66–7:1, 7:56–57, 8:1–2).

Additionally citing Grint's disclosure that methotrexate should be "compounded for convenient and effective administration in effective amounts," Petitioner, supported by Dr. Schiff, contends that one of ordinary skill in the art "would have understood Grint to disclose subcutaneous administration of [methotrexate] in concentrations greater than 30 mg/ml for the treatment of inflammatory autoimmune diseases." Pet. 16–17 (citing Ex. 1003, 6:60–61; Ex. 1034 ¶¶ 49–53). On one hand, Dr. Schiff testifies that one of ordinary skill in the art "would have recognized that a 35 mg/ml concentration of [methotrexate] (within the range disclosed by Grint) could be used to administer a 35 mg dose (within the 'preferred' dosage range disclosed by Grint) using a 1 ml solution . . . consistent with Grint's teaching that methotrexate should be 'compounded for convenient and effective

administration in effective amounts.'" Ex. 1034 ¶ 52 (quoting Ex. 1003, 6:60–61). Similarly, Petitioner contends that one of ordinary skill in the art would have known that "the higher concentrations of [methotrexate] disclosed in Grint, such as 35 mg/ml, should be paired with the higher dosages . . . disclosed in Grint, such as 35 mg, in order to administer [methotrexate] in 'effective amounts,' such as 1 ml." *Id.* at 18 (citing Ex. 1033 ¶ 46; Ex. 1034 ¶¶ 53–55). On the other hand, Petitioner argues that Grint's "reference to 'conventional practice' comes in the context of administration forms [i.e., modes], not concentration levels, and would not have dissuaded the skilled artisan from subcutaneously administering the more than 30 mg/ml concentrations disclosed in Grint." *Id.* (citing Ex. 1034 ¶ 56).

Patent Owner argues that Grint does not disclose the elements of the challenged claims, much less their arrangement as in the claims (PO Resp. 17–22), and that Grint's disclosure of using methotrexate in a "convenient and effective" way is so broad and generic as to provide no information to one of ordinary skill in the art about how to compound or administer it (*id.* at 19). In particular, Patent Owner contends that "Grint never correlates any [methotrexate] concentration with any mode of administration—including parenteral, intraperitoneal, or intravenous." *Id.* at 18. Patent Owner explains that Grint refers to subcutaneous administration only in Example 1, but Example 1 is silent about methotrexate concentration. *Id.* at 19. Patent Owner notes that Dr. Schiff cites Grint's "reference to 'convenient and effective administration'" together with Grint's Example 1 (disclosing a methotrexate dose of 12.5–25 mg/week (Ex. 1003, 7:56–57)) as the basis for his conclusion that "Grint's teachings 'could be used to administer a 35 mg

dose,'" but contends that Dr. Schiff "never says he used such a dose or points to where in Grin[t] that teaching is to be found." *Id.* at 21 (citing Ex. 1034 ¶¶ 51–52.

Moreover, Patent owner's witness, Dr. Massarotti, testifies that parenteral administration encompasses at least eighteen different modes of administration that avoid or circumvent the gastrointestinal tract, including intravenous, intramuscular, subcutaneous, intrathecal, intraperitoneal, etc. Ex. 2018 ¶ 22. Patent Owner argues that Petitioner "never even tries to suggest that Grint correlated a specific concentration . . . with any of those eighteen parenteral modes of administration" or even any of the modes of parenteral administration specifically disclosed in Grint. PO Resp. 20. According to Patent Owner and Dr. Massarotti, one of ordinary skill in the art would have recognized that different modes of administration have different concentration limits for methotrexate. *Id.*; Ex. 2018 ¶ 23. For instance, Dr. Massarotti provides examples of administration of intrathecal injections of methotrexate at 1 mg/ml and subcutaneous injections of methotrexate at 50 mg/2 ml (i.e., 25 mg/ml). Ex. 2018 ¶ 23 (citing Ex. 1021, 24; Ex. 2001,[11] 5).

With respect to Grint's teaching that methotrexate "may be administered in a manner as is conventionally practiced" (Ex. 1003, 5:22–23), Patent Owner asserts that one of ordinary skill in the art would not have understood from Grint that it was conventional practice to administer methotrexate subcutaneously at a concentration above 30 mg/ml. PO Resp.

[11] D. Kurnik et al., *Bioavailability of Oral vs. Subcutaneous Low-Dose Methotrexate in Patients with Crohn's Disease*, 18 ALIMENTARY PHARMACOLOGY & THERAPEUTICS 57 (2003) (Ex. 2001).

16, 23–24. Rather, Dr. Massarotti and Dr. Zizic testify that the standard, i.e., conventional, practice was to administer methotrexate subcutaneously at concentrations of 25 mg/ml or less. Ex. 2018 ¶¶ 17, 25–26, 33; Ex. 2092 ¶¶ 17, 28, 31. Patent Owner contends that Petitioner provides no evidence of any instance before the priority date of the '231 patent in which methotrexate was actually administered subcutaneously at a concentration above 30 mg/ml to treat an inflammatory autoimmune disease. PO Resp. 15–16, 23. Notably, Dr. Miller "testifies that a person of ordinary skill in the art would have wanted to use the higher concentration of [methotrexate] solution," but never testifies that he had prepared a methotrexate solution for subcutaneous administration at a concentration above 30 mg/ml prior to 2006. Ex. 1033 ¶ 60. Similarly, Dr. Schiff admitted that he never subcutaneously administered such a methotrexate solution. Ex. 1034 ¶ 123. Patent Owner further disagrees with Petitioner that Grint's reference to "conventionally practiced" is limited to administration modes and does not apply to concentration levels. *Id.* at 24–25.

Furthermore, Patent Owner argues that when a patent claims a numerical range, and the prior art discloses its own numerical range that overlaps the claimed range, the "prior art is only anticipatory if it describes the claimed range with sufficient specificity such that a reasonable fact finder could conclude that there is no reasonable difference in how the invention operates over the ranges." PO Resp. 25–26 (quoting *Ineos USA LLC v. Berry Plastics Corp.*, 783 F.3d 865, 869 (Fed. Cir. 2015)). Patent Owner argues that it is Petitioner's burden to show that there is no reasonable difference in how the method of the challenged claims would operate over Grint's 0.1–40 mg/ml range, and Petitioner has failed to make

that showing. *Id.* at 26. Also, Patent Owner alleges that combining Grint's dose range (0.1–400 mg) and concentration range (0.1–40 mg/ml) results in volumes between 0.025 ml and 4,000 ml, and at the high and low ends of Grint's resulting volume range, there are marked differences in how the claimed method operates. *Id.* at 26–27. Furthermore, Patent Owner argues, that given concerns relating to toxicity at the injection site, one of ordinary skill in the art would have been cautious about increasing concentration for subcutaneous injection. *Id.* at 29 (citing Ex. 2092 ¶ 26).

In its Reply, Petitioner argues that the testimony of both Dr. Schiff, and Patent Owner's own expert, Dr. Zizic, establishes that Grint anticipates claim 1. Reply 3–6. Petitioner specifically points to Dr. Zizic's testimony that one of ordinary skill in the art would have known, before the priority date of the '231 patent, that it would have been both convenient and effective to subcutaneously administer a 35 mg/ml concentration methotrexate solution to deliver a 35 mg dose of methotrexate using a 1 ml solution. *Id.* at 4–5 (citing Ex. 1039, 111:8–24).

Petitioner criticizes Patent Owner's argument that before the priority date of the '231 patent, no one used methotrexate at concentrations above 25 mg/ml to subcutaneously treat rheumatoid arthritis for two reasons—first, because the absence of a commercial embodiment of the claim predating its priority date does not negate anticipatory teachings of prior art publications, and second, because Dr. Zizic admitted at his deposition that, before the priority date of the '231 patent, he had thought of administering methotrexate in concentrations above 25 mg/ml to his patients, and wanted to do so, but could not only because he did not have access to such solutions. *Id.* at 2, 7–10 (citing Ex. 1039, 114:15–115:2).

As to toxicity concerns, Petitioner argues that Dr. Zizic's testimony demonstrates that one of ordinary skill in the art would not have been so concerned about potential tissue irritation concerns so as to forego the use of methotrexate solutions in concentrations above 30 mg/ml. *Id.* at 11–13 (citing Ex. 1039, 119:10–122:6, 135:8–136:3). And, in regard to the issue of an overlapping range in the anticipating context, Petitioner argues that Patent Owner carries the burden of establishing the criticality of a claimed range in order to avoid a finding that an overlapping range recited by the prior art anticipates. *Id.* at 15 (citing *Ineos*, 783 F.3d at 871). In any event, Petitioner argues that the recited ranges in dependent claims 2 and 22 are not critical, and there is no evidence in the disclosure of the '231 patent that the recited ranges are critical. *Id.* at 16 (citing Pet. 21).

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros., Inc. v. Union Oil Co.*, 814 F.2d 628, 631 (Fed. Cir. 1987). Petitioner does not argue that Grint inherently anticipates claim 1, but instead relies on Grint's express disclosures for its anticipation contention. *See* Pet. 12–17; Reply 3–13. In this regard, Grint generally discloses administering methotrexate in a concentration range of about 0.1 mg/ml to about 40 mg/ml (Ex. 1003, 6:66–7:1) and elsewhere discloses subcutaneous administration of methotrexate (*id.* at 7:56–57, 8:1–2).

For Grint to anticipate the requisite methotrexate concentration and the subcutaneous mode of administration must be "arranged as in the claim." *See Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1369 (Fed. Cir. 2008) ("[A] prior art reference—in order to anticipate under 35 U.S.C. § 102—must not only disclose all elements of the claim within the four

corners of the document, but must also disclose those elements 'arranged as in the claim.'" (quoting *Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 1548 (Fed. Cir. 1983))). Word-for-word identity is not required and the analysis allows for some flexibility. *Microsoft Corp. v. Biscotti, Inc.*, 878 F.3d 1052, 1070-71 (Fed. Cir. 2017). That is, the reference need not "'expressly spell out' all the limitations arranged or combined as in the claim, if a person of skill in the art, reading the reference, would 'at once envisage' the claimed arrangement or combination." *Kennametal, Inc. v. Ingersoll Cutting Tool Co.*, 780 F.3d 1376, 1381 (Fed. Cir. 2015) (quoting *In re Petering*, 301 F.2d 676, 681 (CCPA 1962)). Here, because claim 1 requires subcutaneously administering methotrexate in a concentration of more than 30 mg/ml (Ex. 1001, 8:44–47), for Grint to anticipate, one of ordinary skill in the art must at once envisage the upper values of Grint's disclosed concentration range—i.e., above 30 mg/ml—to be correlated with subcutaneous administration.

Having considered the arguments and evidence presented by both parties, we conclude that Petitioner has not proven by a preponderance of the evidence that Grint anticipates independent claim 1. Our reasoning is as follows.

As discussed above, Grint discloses parenteral administration of methotrexate generally, and intraperitoneal, intravenous, intramuscular, and subcutaneous administration specifically. Ex. 1003, 5:64–65, 7:5, 7:56–57, 8:1–2. Grint further discloses that methotrexate "may be administered as conventionally practiced," citing Goodman as an example, and Goodman additionally discloses intrathecal administration. Ex. 2019, 1266. Dr. Massarotti testifies that parenteral administration includes at least eighteen

different modes of administration—including each of the modes of administration identified in Grint and Goodman—and that it was known as of the priority date of the '231 patent that different modes of parenteral administration were used clinically with different concentrations of methotrexate. Ex. 2018 ¶¶ 22–23 (citing Ex. 1021, 24; Ex. 2001, 5). Dr. Massarotti's testimony on this point is unrebutted, and furthermore, Petitioner identifies no evidence of record that would support a finding that one of ordinary skill in the art would have had a basis to assume that, in Grint, the same methotrexate concentration ranges apply to each mode of parenteral administration.

Accordingly, we agree with Patent Owner that one of ordinary skill in the art would not have understood all of the points within Grint's disclosed concentration range to be applicable to each mode of methotrexate administration disclosed in Grint. *See* PO Resp. 20. Petitioner must therefore show that the higher concentrations of Grint's range of about 0.1 mg/ml to about 40 mg/ml—namely, the concentrations greater than 30 mg/ml—would have been understood by one of ordinary skill in the art as applicable to subcutaneous administration in particular.

Dr. Massarotti and Dr. Zizic testify that the conventional practice in the art was to administer methotrexate subcutaneously in concentrations of 25 mg/ml or less. Ex. 2018 ¶¶ 17–18, 24, 26; Ex. 2092 ¶¶ 17, 28. Specifically, Dr. Massarotti testifies that to her knowledge, "no document published prior to July 21, 2006 reports the actual subcutaneous administration of methotrexate at a concentration greater than 25 mg/ml," nor is she "aware of any others who have administered methotrexate subcutaneously for an inflammatory autoimmune disease or any other

condition at a concentration greater than 25 mg/ml prior to July 21, 2006." Ex. 2018 ¶ 25. Similarly, Dr. Zizic testifies that in his experience, "before the July 21, 2006 priority date of the '231 Patent . . . the highest concentration of methotrexate that I ever used for subcutaneous injection, in treating inflammatory autoimmune disease like rheumatoid arthritis, was 25 mg/ml," and he is "also unaware of other physicians using any higher concentrations subcutaneously for the treatment of inflammatory autoimmune disease before" the priority date. Ex. 2092 ¶ 17. This testimony is consistent with the practice of Petitioner's witness, Dr. Schiff, who testifies that he prescribed doses of methotrexate for subcutaneous administration in concentrations of 25 mg/ml. Ex. 1034 ¶ 123. Dr. Massarotti and Dr. Zizic each conclude that one of ordinary skill in the art reading Grint's disclosed concentration range of about 0.1 mg/ml to about 40 mg/ml would not have understood Grint to be referring to any higher concentrations than 25 mg/ml for the treatment of inflammatory autoimmune diseases using subcutaneous administration. Ex. 2018 ¶ 41; Ex. 2092 ¶ 28.

We find the conclusions of Dr. Zizic and Dr. Massarotti to be better supported than that of Petitioner's expert, Dr. Schiff. According to Dr. Schiff:

> [A] skilled artisan would . . . have understood Grint to disclose the subcutaneous administration of [methotrexate] in concentrations above 30 mg/ml for the treatment of inflammatory autoimmune diseases. For instance, the skilled artisan would have recognized that a 35 mg/ml concentration of [methotrexate] (within the range disclosed by Grint) *could* be used to administer a 35 mg dose (within the "preferred" dosage range disclosed by Grint) using a 1 ml solution. Such a formulation would be consistent with Grint's teaching that

> methotrexate should be "compounded for convenient and effective administration in effective amounts."

Ex. 1034 ¶ 52 (emphasis added) (quoting Ex. 1003, 6:60–61).

Nevertheless, whether one of ordinary skill in the art would have recognized that a 35 mg/ml concentration *could* be used is not sufficient to establish anticipation. *See Therasense, Inc. v. Becton, Dickinson & Co.*, 593 F.3d 1325, 1332 (Fed. Cir. 2014) ("[T]he instruction is incorrect because it makes sufficient, for purposes of anticipation, a prior art disclosure of individual claim elements that 'could have been arranged' in a way that is not itself described or depicted in the anticipatory reference.").

Although a 35 mg dose is within Grint's "preferred" range for a unit dosage form (Ex. 1003, 6:65), the only embodiment in Grint that discloses subcutaneous administration (i.e., Example 1) is tied to a dose of 12.5–25 mg/week (*id.* at 7:56–57). Dr. Schiff's testimony, in focusing on a 35 mg dose, does not address the issue of what concentrations one of ordinary skill in the art would have understood to have been used with the doses of 12.5–25 mg/week that are disclosed in Example 1—the only instance where subcutaneous administration is disclosed in Grint.

Similarly, Dr. Schiff also refers to "using a 1 ml solution,"[12] but his testimony does not cite to where Grint discloses this particular volume, apart

[12] At oral argument, Petitioner's counsel asserted that "there was a motivation in the art, and everyone knew about it, to stay within one milliliter," to obtain "advantages in terms of pain tolerance and things like that, and that has ongoing advantages in terms of people staying with their medication and so forth." Tr. 12:24–13:1. This argument is a consideration relevant to obviousness, not anticipation. *See Eli Lilly & Co. v. L.A. Biomedical Research Inst. at Harbor-UCLA Med. Ctr.*, 849 F.3d 1073, 1075 (Fed. Cir. 2017) (affirming holding that claims were not anticipated where

from suggesting that it falls within the range of Grint's "effective amounts." *See* Ex. 1034 ¶¶ 54, 56. Petitioner argues that Dr. Zizic's testimony confirms that a 1 ml solution is an effective amount. Reply 4–5 (citing Ex. 1039, 111:8–24). Nevertheless, we note that Dr. Zizic further testifies: "In my opinion, the mere statement that a drug should be 'compounded for convenient and effective administration in effective amounts' does not inform a [person of ordinary skill in the art] of any particular doses or concentrations for that drug." Ex. 2092 ¶ 28.

Moreover, we find Grint's disclosure regarding "convenient and effective administration in effective amounts" is, at most, disclosure of a broad genus with limits that are not defined. The testimony of Dr. Schiff and Dr. Zizic establishes that a 1 ml volume falls within that genus, but Petitioner does not establish the size of the genus. *See Wasica Fin. GmbH v. Cont'l Auto. Sys., Inc.*, 853 F.3d 1272, 1285–86 (Fed. Cir. 2017) (explaining that there are situations where a prior art genus may anticipate a later species such as "when the genus is so small that one of ordinary skill in the art would 'at once envisage each member of this limited class,'" but finding that an *inter partes* review petitioner did not show how such a situation exists where the petitioner did not, among other things, establish the size of the genus (quoting *AbbVie Inc. v. Mathilda & Terence Kennedy Inst. of Rheumatology Tr.*, 764 F.3d 1366, 1379 (Fed. Cir. 2014))).

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argument presented in support of anticipation was "at best, . . . an obviousness argument"); *see also Callaway Golf Co. v. Acushnet Co.*, 576 F.3d 1331, 1347 (Fed. Cir. 2009) (explaining that evidence "concerning motivation to combine and obviousness . . . is inapplicable to [an] anticipation argument, where motivation to combine is not an issue").

In contrast to Dr. Schiff's testimony, the opinions of Dr. Massarotti and Dr. Zizic are based on their knowledge of conventional practice. Ex. 2018 ¶ 26; Ex. 2092 ¶ 31. Evidence of conventional practice is relevant to understanding Grint's disclosure because Grint teaches that methotrexate "may be administered in a manner as is conventionally practiced." Ex. 1003, 5:21–22. Dr. Massarotti testifies that "standard practice in the field at [the] time [of the invention], and in my own experience, was to administer subcutaneous methotrexate at concentrations of 25 mg/ml or less." Ex. 2018 ¶ 26. Dr. Massarotti opines that "a skilled artisan reading Grint as of July 21, 2006, would have understood the recitation in Example 1 of Grint—dosing methotrexate at '12.5–25 mg/week (oral, subcutaneous or intramuscular)'—as consistent with what was conventional practice" and would, therefore, have understood that "to administer the 25 mg maximum methotrexate dose of Example 1, an appropriate number of tablets or a 1 ml intramuscular or subcutaneous injection would have been used." *Id.* Along similar lines, Dr. Zizic notes that "Grint refers to 'subcutaneous' only once: in Example 1 ('oral, subcutaneous or intramuscular')' and "does not correlate any such administration to concentration or dose . . . but "says only that a dose of 12.5–25 mg was used." Ex. 2092 ¶ 31. Dr. Zizic testifies "in my view, the [person of ordinary skill in the art] would take from this disclosure that the standard, conventional dose and concentration were being used: up to 25 mg/week using up to 25 mg/ml." *Id.* We credit Dr. Zizic's testimony that a person of ordinary skill in the art "reading Grint would not understand that it was referring to any higher concentrations than 25 mg/ml for the treatment of inflammatory autoimmune diseases using subcutaneous administration." *Id.*

Moreover, Dr. Zizic elaborates that Grint's Example 1 discloses a completed study in which patients received the therapeutic dose of methotrexate beginning four months before the study. *Id.* ¶ 29 (citing Ex. 1003, 7:55–59). Dr. Zizic again persuasively concludes that one of ordinary skill in the art would have understood the patients to have received the methotrexate subcutaneously in concentrations of 25 mg/ml or less because those were the only concentrations of methotrexate used to treat rheumatoid arthritis as of Grint's priority date. *Id.*

We note Petitioner's and Dr. Schiff's argument that Grint's reference to "conventional[] practice[]" pertains to modes of administration (e.g., orally or parenterally), and not to methotrexate concentrations. Pet. 18; Ex. 1034 ¶ 56. We do not, however, read Grint's teaching that methotrexate "may be administered in a manner as is conventionally practiced" to be narrowly limited to modes or routes of administration. As an illustration of how methotrexate "may be administered in a manner as is conventionally practiced," Grint cites to a page of Goodman (Ex. 1003, 5:22–24), which goes beyond a discussion of routes of administration and also discusses preparations and dosages (Ex. 2019, 1266 ("Preparations, Dosage, and Routes of Administration")).

Furthermore, the passage from Grint that Dr. Schiff relies on as the basis for his opinion—i.e., column 5, lines 21–42 (Ex. 1034 ¶ 56)—refers to concentrations of methotrexate in various compositions and preparations—specifically "at least 0.5% of methotrexate," with an instruction that the percentage may "be varied and may conveniently be between about 2 to 60% of the weight of the unit" (Ex. 1003, 5:33–37). We view Grint's disclosures of "at least 0.5% of methotrexate" and "about 2 to 60% of the

weight of the unit" to be indicative of concentrations (*see* Tr. 8:16–17 (Petitioner's counsel, stating that "the concentration is the amount of th[e] drug in a solution of water or saline or something else"); *id.* at 46:18–22 (Patent Owner's counsel, stating that "at least 0.5 percent . . . is 5 [mg/ml]")). Accordingly, we disagree with Dr. Schiff's conclusion that Grint's reference to conventional practice "does not come in the context of a discussion of [methotrexate] concentrations." Ex. 1034 ¶ 56. In other words, we disagree that one of ordinary skill in the art would have understood Grint's reference to conventional practice to refer exclusively to mode of administration, and not to concentration as well.

Petitioner also directs us to Dr. Zizic's deposition testimony where he acknowledges that, before the priority date of the '231 patent, he had wanted to administer methotrexate in concentrations above 25 mg/ml to his patients, in order to avoid the necessity of the patient visiting the clinic to receive an intramuscular injection or to administer multiple self-injections. Reply 8–10 (citing Ex. 1039, 114:15–22). According to Petitioner, this testimony corroborates Dr. Schiff's testimony that he did not have any concerns, doubts, or misgivings about the safety, efficacy, or advantages of using a methotrexate solution more concentrated than 25 mg/ml. *Id.* at 10 (citing Ex. 1034 ¶ 123). But evidence of Dr. Zizic's desire to administer methotrexate subcutaneously in concentrations above 25 mg/ml, along with Dr. Schiff's lack of concern with that approach, falls short of establishing that it was conventional to do so. Instead, the testimony of Dr. Zizic and Dr. Schiff supports the opposite conclusion that it was not conventional practice to administer methotrexate in concentrations above 25 mg/ml. As Petitioner points out, Dr. Zizic testified that such solutions were not available at the

relevant time (*id.* at 8–9 (citing Ex. 1039, 114:23–115:2)), and Dr. Schiff states that the methotrexate solutions that he prescribed and were available to him were in the 25 mg/ml format (Ex. 1034 ¶ 123).[13]

Petitioner contends that Dr. Zizic's testimony also demonstrates that one of ordinary skill would not have doubted that Grint teaches administering methotrexate subcutaneously in concentrations above 30 mg/ml for treating inflammatory autoimmune diseases. Reply 10. Dr. Zizic's testimony, however, concerns why one would have been motivated to administer concentrations above 25 mg/ml. *See* Ex. 1039, 114:15–22. That issue—whether one would have been motivated to select certain concentrations within the disclosed concentration range—is pertinent to an obviousness inquiry, as opposed to the anticipation ground brought by Petitioner.

Although extrinsic evidence may be considered in the anticipation context for purposes of educating the decision-maker as to what a reference meant to persons of ordinary skill in the field of invention, such factual elaboration is of limited scope and probative value, and may not be used to fill gaps in the reference. *Scripps Clinic & Research Found. v. Genentech, Inc.*, 927 F.2d 1565, 1576 (Fed. Cir. 1991), *overruled on other grounds by Abbott Labs. v. Sandoz, Inc.*, 566 F.3d 1282, 1293 (Fed. Cir. 1993). Accordingly, we credit the expert testimony to the extent it addresses how one of ordinary skill in the art would have understood what is disclosed in Grint—for example, the meaning of "conventional[] practice" and how one

[13] Regarding Petitioner's argument that anticipation does not require proof of a commercial embodiment existing before the priority date (Reply 8), we agree (*see, e.g.*, *Schering Corp. v. Geneva Pharm., Inc.*, 339 F.3d 1373, 1380 (Fed. Cir. 2003)), but the argument is beside the point in this instance.

of ordinary skill in the art would have understood Grint's Example 1 to be a completed study within the conventional practice of subcutaneous administration. Ex. 2092 ¶¶ 28–29, 31. We may not, however, use expert testimony to fill in gaps in Grint—here, a missing link between the upper values of Grint's disclosed concentration range and the applicability of those values particularly to subcutaneous administration. In any event, even when considering all of Dr. Zizic's testimony, we give less weight to Dr. Zizic's unpublished prior thoughts regarding an unavailable procedure that he did not practice, as compared to his opinions addressing Grint's disclosures.

At oral argument, Petitioner's counsel argued that the upper portions (i.e., 30 mg/ml or higher) of Grint's disclosed concentration range would have been used for subcutaneous administration because "the only options are subcutaneous and intramuscular" and "subcutaneous and intramuscular are interchangeable." Tr. 13:9–14:12. It is only the case for Grint's Example 1, however, that subcutaneous and intramuscular administration are given as the only options for parenteral administration. Again, we do not agree that Grint's disclosure of a concentration range of about 0.1 mg/ml to about 40 mg/ml to be linked or directly related to Example 1. Instead, Grint's teaching referencing that concentration range is part of a general discussion concerning the administration of methotrexate that also discloses other modes of administration apart from subcutaneous and intramuscular administration. *See* Ex. 1003, 5:22–7:13. Within that discussion, Grint refers to parenteral, intraperitoneal, and intravenous administration. *Id.* at 5:64–65. Additionally, Grint cites to Goodman as an example of administering methotrexate (*id.* at 5:22–23), and Goodman further references intrathecal administration (Ex. 2019, 1266). As Dr. Massarotti

testifies, parenteral administration includes at least eighteen different types of administration (including subcutaneous, intramuscular, intraperitoneal, intravenous, and intrathecal). Ex. 2018 ¶ 22.

Petitioner has not shown that subcutaneous administration was known to be used in the same concentration ranges as all of the other modes of parenteral administration in Grint, or even that subcutaneous administration was known to be used at higher concentrations than the other modes of administration such that one of ordinary skill in the art would envisage the highest values within Grint's disclosed concentration range to apply to subcutaneous administration. Accordingly, Petitioner has not proven by a preponderance of the evidence that one of ordinary skill in the art would have envisioned the upper portions of Grint's disclosed concentration range (i.e., from 30 mg/ml to 40 mg/ml) to apply specifically to subcutaneous administration, as opposed to the other modes of parenteral administration in Grint.

The parties also dispute whose burden it is to show the criticality of a claimed range where the prior art discloses an overlapping range in an anticipation challenge. *Compare* PO Resp. 26 (arguing that it is the petitioner's burden) *with* Reply 15 (arguing that it is the patent owner's burden). Here, Grint discloses a concentration range of "about 0.1 to about 40 mg/ml" (Ex. 1003, 6:66–67), and the '231 patent's claim 1 is directed to a concentration of "more than 30 mg/ml" (Ex. 1001, 8:47). Because Petitioner has not shown by a preponderance of the evidence that Grint discloses an overlapping range that pertains in particular to subcutaneous administration as required by the '231 patent's claims in the first instance, the issues of whether Grint describes the claimed range with sufficient specificity and the

criticality of the claimed range (as well as the parties' burdens with respect to those issues) are not relevant in this case. For that reason, we do not further address the parties' arguments regarding whether Grint's disclosure of an overlapping concentration range is sufficient to anticipate.

Petitioner also argues that Grint anticipates dependent claims 2, 4–6, 11–13, 17, and 22 of the '231 patent. Pet. 14–16, 19–22. These claims depend directly or indirectly from claim 1, further narrowing the concentrations encompassed by claim 1—adding limitations regarding the pharmaceutically acceptable solvent, the types of inflammatory autoimmune diseases treated, or specifying a storage container. Ex. 1001, 8:48–50, 8:53–64, 9:8–14, 10:4–5, 10:18–20. As we find that Petitioner has not proven by a preponderance of the evidence that Grint anticipates claim 1, we also find that Petitioner has not proven by a preponderance of the evidence that Grint anticipates claims 2, 4–6, 11–13, 17, and 22 for the same reasons.

D. Obviousness over Grint, Arthur, Moitra, and Insulin Admin., and Obviousness over Grint and Alsufyani

We also instituted *inter partes* review on obviousness grounds—specifically, (i) whether claims 7–10, 14–16, and 19–21 would have been obvious over Grint, Arthur, Moitra, and Insulin Admin., and (ii) whether claim 18 would have been obvious over Grint and Alsufyani. Inst. Dec. 36–37. Each of claims 7–10, 14–16, and 19–21 depends directly or indirectly from claim 1, and recites additional limitations regarding self-administration, an injection device for a single application, dosage amounts, a carpule as a storage container, and a pen injector for multiple applications. Ex. 1001, 8:65–9:7, 9:15–10:3, 10:8–17. Claim 18 recites treatment of juvenile rheumatoid arthritis. *Id.* at 10:6–7.

"Even if a reference's teachings are insufficient to find anticipation, that same reference's teachings may be used to find obviousness." *CRFD Research, Inc. v. Matal*, 876 F.3d 1330, 1345 (Fed. Cir. 2017). Here, however, Petitioner's obviousness arguments rely on Grint as expressly disclosing the elements of claim 1. Petitioner relies on the Arthur, Moitra, Insulin Admin., and Alsufyani as teaching the additional limitations recited in claims 7–10, 14–16, and 18–21, not to show that the concentration values in the upper portion of Grint's concentration range (i.e., above 30 mg/ml) would have been understood to apply to subcutaneous administration. *See* Pet. 22–30. Accordingly, because Petitioner does not rely on the additional references to cure the deficiencies in Grint, we find that Petitioner has not shown by a preponderance of the evidence that claims 7–10, 14–16, and 19–21 would have been obvious over Grint, Arthur, Moitra, and Insulin Admin., or that claim 18 would have been obvious over Grint and Alsufyani.

E. Anticipation by Wyeth

Petitioner asserts that Wyeth anticipates claims 1–6, 11–13, 17, 18, and 22 of the '231 patent under 35 U.S.C. § 102(b). Pet. 30–38. Patent Owner argues that Wyeth does not disclose the elements of those claims, or their arrangement as in those claims. PO Resp. 30–41.

1. Wyeth

Wyeth is a pharmaceutical label titled "Methotrexate Sodium for Injection," and discloses "Methotrexate Sodium for Injection products . . . given by the intramuscular, intravenous, intra-arterial or intrathecal route." Ex. 1021, 1, 3. Wyeth's lyophilized injection products are available in 20 mg and 1 gram vials. *Id.* at 3, 24–25. In addition, Wyeth discloses methotrexate sodium tablets for oral administration. *Id.* at 23–24.

Wyeth teaches that methotrexate is used in the treatment of neoplastic diseases, psoriasis, adult rheumatoid arthritis, and polyarticular-course juvenile rheumatoid arthritis and discloses dosage and administration schedules for treating each of those conditions. *Id.* at 2, 7, 18–24. Several neoplastic diseases are identified (*id.* at 18–21), including osteosarcoma, in which the starting dose for methotrexate treatment is 12 g/m^2, administered intravenously (*id.* at 20–21). On the other hand, recommended single dosage amounts are 7.5 mg for adult rheumatoid arthritis administered orally, and 10 to 25 mg for psoriasis administered orally, intramuscularly, or intravenously. *Id.* at 23–24. For polyarticular-course juvenile rheumatoid arthritis, Wyeth initially states that "[t]he recommended starting dose is 10 mg/m^2 given once weekly," but that for either adult or juvenile rheumatoid arthritis, dosages may be adjusted gradually to achieve an optimal response. *Id.* at 23.

Wyeth further states:

> Although there is experience with doses up to 30 $mg/m^2/wk$ in children, there are too few published data to assess how doses over 20 $mg/m^2/wk$ might affect the risk of serious toxicity in children. Experience does suggest, however, that children receiving 20 to 30 $mg/m^2/wk$ (0.65 to 1.0 mg/kg/wk) may have better absorption and fewer gastrointestinal side effects if methotrexate is administered either intramuscularly or subcutaneously.

Id.

Wyeth specifies that the 20 mg and 1 gram vials of lyophilized methotrexate sodium for injection are for single use only, and should be reconstituted immediately prior to use. *Id.* at 3, 24, 26. Specifically, the 20 mg vial is to be reconstituted to a concentration of no greater than 25 mg/ml, and the 1 gram vial is to be reconstituted to a concentration of 50 mg/ml. *Id.*

at 24. Wyeth further explains that when high doses of methotrexate are administered intravenously, the total dose is diluted. *Id.*

2. Analysis

Petitioner argues that Wyeth anticipates claim 1 based on Wyeth's disclosure of administering methotrexate to treat psoriasis and rheumatoid arthritis, Wyeth's disclosure of treating polyarticular-course juvenile rheumatoid arthritis by subcutaneous injection, and Wyeth's disclosure that the 1 gram vial of methotrexate should be reconstituted to a concentration of 50 mg/ml. Pet. 31 (citing Ex. 1021, 7, 23–24). According to Petitioner, supported by Dr. Schiff, those disclosures, taken together, "teach[] administering methotrexate to children for the treatment of [juvenile rheumatoid arthritis] in a concentration of 50 mg/ml via subcutaneous injection" and [o]ne of ordinary skill would have understood that teaching to apply equally to adults with other inflammatory autoimmune diseases such as [rheumatoid arthritis]." *Id.* at 34 (citing Ex. 1021, 23–24; Ex. 1034 ¶¶ 74–75).

Petitioner contends that, as Wyeth is a label approved by the U.S. Food & Drug Administration ("FDA"), the FDA had deemed it safe for one of ordinary skill in the art to administer methotrexate in a 50 mg/ml concentration. *Id.* (citing Ex. 1033 ¶ 63); *see also* Ex. 1033 ¶ 63 (Dr. Miller, attesting that based on his experience as a member of the FDA Arthritis Committee, "FDA-approval demonstrates that the FDA had deemed it safe and appropriate for a skilled artisan to administer the [methotrexate] product disclosed in Wyeth in a 50 mg/ml concentration for the treatment of [rheumatoid arthritis], [juvenile rheumatoid arthritis], and psoriasis.").

Petitioner argues that Wyeth's 20 mg vial, which should only be reconstituted to a concentration no greater than 25 mg/ml, is a different product and is irrelevant. *Id.* In this regard, Petitioner directs us to Bigmar,[14] a label for a generic equivalent of Wyeth's 1 gram vial only, pointing out that Bigmar discloses the same concentration of 50 mg/ml. *Id.* at 34–35 (citing Ex. 1026, 6; Ex. 1034 ¶ 79); *see also* Ex. 1034 ¶ 79 (stating that, as Bigmar does not relate to the 20 mg format, Bigmar does not mention a 25 mg/ml concentration limitation). Bigmar also contains an instruction to "[d]iscard unused portion" (Ex. 1026, 7), which according to Petitioner reinforces that the solution was to be administered in a 50 mg/ml concentration and not to be further diluted (Pet. 35 (citing Ex. 1034 ¶ 79)).

Petitioner acknowledges Dr. Zizic's testimony in his declaration in which he stated that one of ordinary skill in the art would have made use of the 20 mg vial to treat inflammatory autoimmune diseases—not the 1 gram vial—but contends that Dr. Zizic, on cross-examination, "testified that his opinion was ***not*** based on the concentration difference between the 20 mg vial product and the 1 gram vial product." Reply 19 (citing 1039, 118:3–6). Petitioner argues that Dr. Zizic testified on cross-examination that one would have used Wyeth's 20 mg vial because it more closely matches the dosages typically administered to treat inflammatory autoimmune diseases than the 1 gram vial, but in the hypothetical situation where the 20 mg vial was unavailable, the only significant consequence of using Wyeth's 1 gram vial to treat a would be to waste most of the reconstituted solution. Reply 19 (citing Ex. 1039, 117:20–118:6; 119:10–122:6

[14] Bigmar, Inc., Methotrexate for Injection USP (1999) (Ex. 1026, "Bigmar").

Petitioner further argues that Dr. Zizic also testified on cross-examination that once a person of ordinary skill in the art had developed comfort with a given dosage of methotrexate, such as 25 mg, that person would not have had serious concerns about administering a 50 mg/ml concentration solution instead of a 25 mg/ml concentration solution. Reply 20 (citing Ex. 1039, 135:8–136:3). Moreover, Petitioner states that Dr. Zizic agreed that if a methotrexate product had been approved by the FDA for the treatment of inflammatory autoimmune diseases in a concentration of 50 mg/ml, one of ordinary skill in the art would have understood that product to have been safe and effective if used according to the label. *Id.* (citing Ex. 1039, 138:7–23).

In response, Patent Owner emphasizes that Wyeth discloses two different methotrexate products: a 20 mg vial and 1 gram vial, and provides different reconstitution instructions for each product. PO Resp. 32. Specifically, the 20 mg vial is to be "reconstituted to 'a concentration *no greater than* 25 mg/mL,' leading to a minimum volume of 0.8 ml," (*id.* at 33 (citing Ex. 1021, 79)), while the 1 gram vial is to be "reconstituted with 19.4 mL to a concentration of 50 mg/mL" (*id.* at 33 (citing Ex. 1021, 79)). Patent Owner contends "this is the only reference to 50 mg/ml—or any concentration over 25 mg/ml—in all of Wyeth." *Id.*

Patent Owner contends that the 1 gram vial is not used for subcutaneous administration for inflammatory autoimmune diseases, but instead for intravenous administration in the treatment of cancer, and only after further dilution from the initial 50 mg/ml concentration. *Id.* at 17, 33–36 (citing Ex. 2018 ¶¶ 49–55; Ex 2092 ¶¶ 35–37; Ex. 2093 ¶¶ 18, 20–22). Patent Owner argues that it is incorrect to conclude that Wyeth teaches that

the 50 mg/ml concentration can be used for any mode of administration mentioned in the label, and that Wyeth expressly states to use only 1 mg/ml for intrathecal administration. *Id.* (citing Ex. 2018 ¶ 23). Also, Patent Owner points out that Wyeth teaches that the vials (whether 20 mg or 1 gram) are for "Single Use Only" and that if a rheumatoid arthritis patient were to be treated with a single weekly dose of 25 mg, using a 1 gram vial would result in wasting 975 mg (i.e., 97.5%) of the drug. *Id.* at 33–34 (quoting Ex. 1021, 3, 25) (citing Ex. 2018 ¶ 56; Ex. 2093 ¶ 22).

Additionally, Patent Owner argues that Wyeth does not indicate that methotrexate should be injected subcutaneously, but rather, should be administered through other routes, except in a specific case for children. PO Resp. 32. Patent Owner contends that a passing reference to subcutaneous injection in children at a particular dose would not inform one of ordinary skill in the art that such subcutaneous injection could be used with any concentration and any disease. *Id.*

In any case, Patent Owner argues that only the 20 mg vial would make sense for rheumatoid arthritis treatment as this dosage, and the resulting volume when reconstituted at 25 mg/ml, would be within amounts that were appropriate for subcutaneous injection in the treatment of inflammatory autoimmune diseases. *Id.* at 35 (citing Ex. 1021, 24; Ex. 2018 ¶¶ 18, 54; Ex. 2092 ¶¶ 18, 30, 37; Ex. 2093 ¶ 21). Further, Patent Owner contends that Wyeth discloses larger doses—for example, 1.7 g for treatment of acute lymphoblastic leukemia and 20.4 g for treatment of osteosarcoma—and that one of ordinary skill in the art would understand that the 1 gram vials would be used for those applications. *Id.* at 35–36 (citing Ex. 1021, 11, 14, 20–21; Ex. 2092 ¶ 36; Ex. 2093 ¶ 20).

In addition, Patent Owner cites SICOR,[15] an Abbreviated New Drug Application Suitability Petition filed with the FDA by SICOR Pharmaceuticals, Inc., as evidence that one of ordinary skill in the art would have known that 1 gram methotrexate vials were to be used exclusively for treating osteosarcoma intravenously. PO Resp. 36–37 (citing Ex. 2018 ¶¶ 58–59; Ex. 2021, 1). SICOR is directed to a single-use vial containing 1 gram of a methotrexate injection as a ready-to-use liquid in a concentration of 100 mg/ml. Ex. 2021, 1–2. SICOR compares that product with a reference product approved for Bedford Laboratories—a 1 gram single-use vial with instructions to reconstitute to a concentration of 50 mg/ml, as in Wyeth. *Id.* SICOR states that the approved label for the reference product describes intramuscular and intravenous dosage regimens for the treatment of choriocarcinoma and similar trophoblastic diseases (up to 30 mg daily), arthritis (10 mg/m^2 every week), and psoriasis (10 mg to 25 mg per week), and a "High Dose Regimen" for treatment of osteosarcoma in amounts of 12 grams/m^2 to 15 grams/m^2. *Id.* at 3. SICOR then states: "Based on information included in the approved labeling, it is presumed that the [1 gram] size is used exclusively for preparing the High Dose Regimen." *Id.* Patent Owner states that this objectively confirms that Petitioner's reading of Wyeth—i.e., that the 1 gram vial is used for the treatment of psoriasis or for intramuscular or subcutaneous injection—is not consistent with how one of ordinary skill in the art would have understood Wyeth. PO Resp. 37.

[15] Letter from Roalie A. Lowe, Authorized Agent, SICOR Pharm., Inc., to Dockets Mgmt. Branch, Food & Drug Admin. (Apr. 28, 2006) (Ex. 2021, "SICOR").

Patent Owner further argues that Wyeth lists many different diseases but does not correlate a particular methotrexate concentration with any of those diseases. *Id.* at 37–38. Also, Patent Owner argues that Dr. Schiff and Dr. Miller do not address the entirety of Wyeth's teachings, most notably Wyeth's admonition to avoid using a concentration higher than 25 mg/ml for the product contained in the 20 mg vial and Wyeth's disclosure regarding intravenous infusion. *Id.* at 38–40. Patent Owner states that FDA approval of Wyeth does not mean that one of ordinary skill in the art would have understood that the separate statements in Wyeth regarding subcutaneous injection and reconstituting the 1 gram vial should be combined. *Id.* at 39–40.

Patent Owner also disputes Petitioner's assertions regarding Bigmar, pointing to instructions in Bigmar regarding dilution for intravenous infusion—Patent Owner argues that one of ordinary skill in the art would have understood those instructions to refer to the general practice of diluting a drug for infusion after reconstituting it according to the label. *Id.* at 38–39 (citing Ex. 1026, 6; Ex. 2093 ¶¶ 23–24). Additionally, Patent Owner disputes Dr. Schiff's claim that Bigmar "does not instruct further dilution prior to administration" given that Bigmar states "[f]or intrathecal injection, reconstitute to a concentration of 1 mg/mL." *Id.* at 39 (alteration in original) (first quoting Ex. 1034 ¶ 79; and then quoting Ex. 1026, 6). Patent Owner further points out that Bigmar lacks any reference to subcutaneous injection. *Id.*

Furthermore, Patent Owner maintains that one of ordinary skill in the art would have understood that subcutaneously injecting methotrexate and other cytotoxic agents at relatively high concentrations could damage

surrounding soft tissue. *Id.* at 40 (citing Ex. 2092 ¶¶ 19–26). Patent Owner argues that one of ordinary skill in the art would have known that there were local toxicity risks when injecting cytotoxic agents like methotrexate, and that those effects could depend on concentration, not just total dose, such that one of ordinary skill in the art would have been cautious about increasing methotrexate concentration above 25 mg/ml. *Id.* at 41.

Having considered the arguments and evidence presented by both parties, we conclude that Petitioner has not proven by a preponderance of the evidence that Wyeth anticipates independent claim 1. Our reasoning is as follows.

We apply the same principles regarding anticipation as set forth above in our analysis of Grint. *See supra* § II.C.2. As with Grint, Petitioner does not contend that Wyeth inherently anticipates claim 1, but instead relies on Wyeth's express disclosures in arguing that Wyeth anticipates. *See* Pet. 30–36; Reply 18–20. In this regard, Petitioner relies on separate parts of Wyeth as disclosing two limitations of claim 1—first, "subcutaneously administering" methotrexate to a patient in need of treatment for an inflammatory autoimmune disease, and second, "at a concentration of more than 30 mg/ml" (Ex. 1001, 8:44–47). Nevertheless, the only instance in which the "subcutaneously administering" limitation is disclosed is in the context of juvenile rheumatoid arthritis, where Wyeth states that experience suggests that children receiving doses of 20 mg/m^2/wk to 30 mg/m^2/wk of methotrexate may have better absorption and fewer gastrointestinal side effects if the methotrexate is administered either intramuscularly or subcutaneously. Ex. 1021, 23. As for the claimed concentration, Wyeth discloses two products, a 20 mg vial and a 1 gram vial, and the only instance

in which a concentration of more than 30 mg/ml is disclosed in Wyeth is in relation to the 1 gram vial. *Id.* at 24. That is, Wyeth discloses that the 1 gram vial should be reconstituted to a concentration of 50 mg/ml (which meets the claimed concentration limitation), but provides an instruction to reconstitute the 20 mg vial to a concentration no greater than 25 mg/ml (which does not meet the claimed concentration limitation). *Id.*

Accordingly, to establish by a preponderance of the evidence that Wyeth anticipates claim 1, Petitioner must establish that there is a link between the disclosure of the *1 gram vial* of methotrexate and the disclosure of subcutaneously administering methotrexate to treat inflammatory autoimmune disease. *See Net MoneyIN*, 545 F.3d at 1370 (summarizing *Ecolochem, Inc. v. Southern California Edison Co.*, 227 F.3d 1361 (Fed. Cir. 2000), as holding that a prior art reference could not anticipate the claimed invention where there was no link between an embodiment illustrated in a figure and a separate passage containing a general discussion). In other words, Wyeth anticipates if the 1 gram vial disclosure is directly related to the subcutaneous administration disclosure. *See Purdue Pharma L.P. v. Epic Pharma, LLC*, 811 F.3d 1345, 1358–59 (Fed. Cir. 2016) (no impermissible combination of disclosures in distinct sections of a prior art reference to find anticipation where the disclosures were directly related). Wyeth, however, need not "'expressly spell out' all the limitations arranged or combined as in the claim, if a person of skill in the art, reading the reference, would 'at once envisage' the claimed arrangement or combination." *Kennametal*, 780 F.3d at 1381 (quoting *Petering*, 301 F.2d at 681).

Based on the full record developed in this proceeding, we determine that Petitioner has failed to establish that one of ordinary skill in the art would envisage the claimed combination, or that there is a link between the 1 gram vial disclosed in Wyeth and Wyeth's disclosure of subcutaneous administration, i.e., that those two disclosures are directly related, for the following reasons.

As discussed above, Dr. Schiff testifies that Wyeth discloses all of the elements of claim 1 (Ex. 1034 ¶¶ 73–76, 82–84), and opines that one of ordinary skill in the art would have understood that Wyeth teaches subcutaneous administration of a 50 mg/ml methotrexate solution for treating inflammatory autoimmune diseases (*id.* ¶ 78). Dr. Schiff's opinion, however, is merely conclusory in that it points to multiple, distinct teachings in Wyeth regarding subcutaneous administration and the 1 gram product reconstituted to 50 mg/ml, without further explanation as to why one of ordinary skill in the art would have envisioned their combination, or how the separate, individual disclosures are linked or directly related. *See id.* ¶¶ 75–76, 78; *see also Net MoneyIN*, 545 F.3d at 1371 ("[I]t is not enough that the prior art reference . . . includes multiple, distinct teachings that the artisan might somehow combine to achieve the claimed invention.").

On the other hand, Dr. Zizic explains why Wyeth's disclosure does not link the 1 gram product—reconstituted to 50 mg/ml—to treatment of inflammatory autoimmune disease by subcutaneous injection. For instance, Dr. Zizic notes that Wyeth discloses dosages that are on the order of grams (*see* Ex. 1021, 20–21 ("12 g/m^2" which "may be escalated to 15 grams/m^2")), and on the order of tens of milligrams (*e.g.*, *id.* at 24 ("10 to 25 mg per week")). Ex. 2092 ¶¶ 35–37. The larger dose on the order of grams

is used for a 4-hour intravenous infusion for treatment of osteosarcoma, while other conditions, including all of the inflammatory autoimmune diseases, are dosed in the smaller amounts on the order of tens of milligrams. *Id.* (citing Ex. 1021, 21, 24). The dosages associated with the disclosure of subcutaneous administration for treating juvenile rheumatoid arthritis range from 20 mg/m^2/wk to 30 mg/m^2/wk. *Id.* (citing Ex. 1021, 23). Those dosages are on the order of tens of milligrams. *See* Ex. 1034 ¶ 70 ("[A] dosage of 30 mg/m^2 applied to a child 56 inches in height and weighing 75 pounds would translate to an approximately 35 mg dose of [methotrexate]." (citing Ex. 1032, 1)).

Accordingly, we credit Dr. Zizic's testimony tending to show that, at most, the preponderance of the evidence demonstrates that Wyeth discloses a link between administering methotrexate subcutaneously to treat rheumatoid arthritis and using the disclosed lower concentration product. *See* Ex. 2092 ¶¶ 35–37; Ex. 1039, 117:20–118:3.

As for Dr. Zizic's testimony under cross-examination that there would have been some basis to conclude that a patient migh tolerate subcutaneous injection of a more concentrated solution, we note that Dr. Zizic also testified that there would have been concerns about increasing the concentration. Ex. 1039, 136:6–138:4. Specifically, Dr. Zizic testified that at the time of the '231 patent, one of ordinary skill in the art would have been concerned that the more concentrated product could be more irritating locally. Ex. 1039, 43:4–13, 44:16–25, 51:20–52:12, 53:7–9.

Moreover, Petitioner's proposed scenario where a clinician has access to the 1 gram vial of methotrexate only, and would hypothetically use it to treat a patient with an autoimmune diseases (thereby wasting approximately

975 mg of the drug) (Ex. 2091 ¶ 37; Ex. 1039, 119:10–122:18), might have some bearing on an obviousness analysis, but is insufficient for purposes of anticipation where, as here, there is no disclosure with sufficient clarity in Wyeth to do so. *See Therasense*, 593 F.3d at 1332 ("[T]he instruction is incorrect because it makes sufficient, for purposes of anticipation, a prior art disclosure of individual claim elements that 'could have been arranged' in a way that is not itself described or depicted in the anticipatory reference."); *Motorola, Inc. v. Interdigital Tech. Corp.*, 121 F.3d 1461, 1473 (Fed. Cir. 1997) ("For a prior art reference to anticipate a claim, the reference must disclose each and every element of the claim with sufficient clarity to prove its existence in the prior art. Although this disclosure requirement presupposes the knowledge of one skilled in the art of the claimed invention, that presumed knowledge does not grant a license to read into the prior art reference teachings that are not there."). There is no situation described in Wyeth—as in the hypothetical proposed to Dr. Zizic—in which the 1 gram vial is the only option available for treatment. On the contrary, Wyeth's instructions are based on the availability of both the 20 mg and 1 gram vials (*see* Ex. 1021, 3, 25).

In any case, Dr. Zizic's testimony on cross-examination as to the hypothetical scenario does not address all of the limitations of claim 1, which requires that the methotrexate be "subcutaneously administer[ed]" and "at a concentration of more than 30 mg/ml" (Ex. 1001, 8:44–47). As Patent Owner's counsel points out, Dr. Zizic's testimony neither establishes what mode of administration he would have used or what the concentration would have been. Tr. 55:12–56:1. For instance, Dr. Zizic's testimony does not establish whether he would have administered the solution prepared

from the 1 gram vial subcutaneously (a mode mentioned only once in Wyeth in relation to the particular example of juvenile rheumatoid arthritis (Ex. 1021, 23)), or by the intramuscular, intravenous, intra-arterial, or intrathecal routes (which are the modes of parenteral administration to which Wyeth is primarily directed (*id.* at 3)). Similarly, Dr. Zizic's testimony does not establish whether he would have administered the product from the 1 gram vial at the reconstituted concentration of 50 mg/ml, or whether he would have further diluted it (similar to the instructions in Wyeth for intravenous and intrathecal use (*id.* at 24)), in order to obtain the 25 mg/ml concentration that is instructed for use with the 20 mg vial (*id.*), and conventionally used with subcutaneous administration. Accordingly, even in the hypothetical scenario in which the 1 gram vial is the only product available to the clinician, Petitioner has not carried its burden to show that the methotrexate would have been administered as required by claim 1.

Finally, we agree with Patent Owner that FDA approval of Wyeth does not mean that one of ordinary skill in the art would have understood that separate statements in the label that are not linked or directly related should be combined. PO Resp. 40. Also, as Petitioner acknowledges and as Dr. Zizic explained, one of ordinary skill in the art would have understood the product to have been safe and effective if used according to the label. Reply 20 (citing Ex. 1039, 138:7–23). Here, the label does not direct the broad use of the "50 mg/ml concentration either subcutaneously or intramuscularly for treating [rheumatoid arthritis], [juvenile rheumatoid arthritis], and psoriasis," as Petitioner alleges (*id.*). Instead, the Wyeth label refers to subcutaneous administration only once, for treating juvenile rheumatoid arthritis, and not in connection with a 50 mg/ml concentration.

Ex. 1021, 23. Even there the label does not definitively confirm that the dose at which methotrexate is administered subcutaneously is completely safe and effective. Rather, the label warns that "there are too few published data to assess how doses over 20 mg/m^2/wk might affect the risk of serious toxicity in children." *Id.*

Accordingly, we agree with Patent Owner that Petitioner has not established persuasively that Wyeth discloses a link between using its 1 gram product, reconstituted to 50 mg/ml, and treating rheumatoid arthritis subcutaneously. At most, the preponderance of the evidence demonstrates that a person of skill in the art would have understood the disclosure as linking Wyeth's 20 mg vial—to be reconstituted to no more than 25 mg/ml—to treatment of rheumatoid arthritis as the volume and dosage are consistent with the dosages disclosed as appropriate for subcutaneous injection in the treatment of inflammatory autoimmune diseases. *Id.* at 35 (citing Ex. 1021, 24; Ex. 2018 ¶¶ 18, 54; Ex. 2092 ¶¶ 18, 30, 37; Ex. 2093 ¶ 21). Consequently, we determine that Petitioner has not established by a preponderance of the evidence that Wyeth anticipates claim 1, which requires subcutaneously administering methotrexate at a concentration of more than 30 mg/ml to a patient in need of treatment of an inflammatory autoimmune disease.

Petitioner also argues that Wyeth anticipates dependent claims 2–6, 11–13, 17, 18, and 22 of the '231 patent. Pet. 30, 32–33, 36–38. Each of these dependent claims depends directly or indirectly from claim 1, either further narrowing the concentrations encompassed by claim 1, or adding limitations regarding the pharmaceutically acceptable solvent, types of inflammatory autoimmune diseases, and a storage container. Ex. 1001,

8:48–64, 9:8–14, 10:4–7, 10:18–20. As we find that Petitioner has not proven by a preponderance of the evidence that Wyeth anticipates claim 1, we also find that Petitioner has not proven by a preponderance of the evidence that Wyeth anticipates claims 2–6, 11–13, 17, 18, and 22 for the same reasons.

F. Obviousness over Wyeth in View of Brooks, Arthur, and Moitra

We also instituted *inter partes* review on whether claims 1–6, 11–13, 17, 18, and 22 are obvious over Wyeth, Brooks, Arthur, and Moitra. Inst. Dec. 36–37.

1. Brooks

Brooks is a journal article comparing the pharmacokinetics of methotrexate after intramuscular and subcutaneous injections in patients with rheumatoid arthritis. Ex. 1008, 91. Brooks states that its "findings suggest that [methotrexate] concentrations achieved by each method of delivery are statistically and clinically similar, and that [intramuscular] and [subcutaneous] injections are interchangeable routes of [methotrexate] administration." *Id*. at 93. Brooks also reports that most patients found the subcutaneous injection less painful than the intramuscular injection. *Id*.

2. Arthur

Arthur discloses the results of a study comparing the safety and efficacy of methotrexate administered by intramuscular and subcutaneous injection to treat rheumatic conditions. Ex. 1023, 256. The study concludes that there is no difference in the safety and efficacy when the drug is given by either parenteral route. *Id*. The study recommends that patients receiving methotrexate intramuscularly should be switched to the subcutaneous route with a view toward self-administering their therapy, and that, in the future,

parenteral methotrexate should be prescribed subcutaneously instead of intramuscularly. *Id.* at 262. Arthur states that patients were able to safely administer methotrexate subcutaneously, and that self-administration reduced hospital visits, was more convenient for patients and improved patient satisfaction. *Id.* at 256–57.

3. Moitra

Moitra describes methotrexate as one of the most widely prescribed anti-rheumatic drugs. Ex. 1025, 256. Moitra states that there are no significant differences between methotrexate administered subcutaneously and intramuscularly, making the two routes interchangeable. *Id.*

4. Analysis

The main difference between Petitioner's anticipation and obviousness challenges based on Wyeth is in regard to the "subcutaneously administering" element of claim 1. In Petitioner's obviousness challenge, Petitioner does not rely on Wyeth, but instead relies on Brooks, Moitra, and Arthur, for the "subcutaneously administering" methotrexate limitation of claim 1. Pet. 39–40, 44–47. Petitioner also relies on Wyeth, Brooks, Arthur, and Moitra as teaching treatment of inflammatory autoimmune diseases, including the specific conditions recited in claims 5 and 6, and the concentration of "more than 30 mg/ml" as required in claim 1 and further narrowed in claims 2, 3, and 22. *Id.* at 38–41, 44, 47. Otherwise, as in Petitioner's anticipation challenge, Petitioner relies solely on Wyeth as disclosing the other elements of claim 1, as well as the elements of claims 4, 11–13, 17, and 18. *Id.* at 41–43.

Patent Owner argues that Wyeth does not disclose the requisite concentration ranges, and Petitioner does not rely on any of the three cited

secondary references to provide that teaching. PO Resp. 48. Patent Owner therefore states that the asserted combination of Wyeth, Brooks, Arthur, and Moitra fails to cure Wyeth's deficiencies. *Id.*

We find that Petitioner has not shown by a preponderance of the evidence that the subject matter of claims 1–6, 11–13, 17, 18, and 22 would have been obvious over Wyeth, Brooks, Arthur, and Moitra. Although Petitioner cites to Brooks, Arthur, and Moitra in connection with its argument that the combined set of references teaches a concentration of more than 30 mg/ml, Petitioner does not point to where any of those references disclose any concentration at all. Pet. 40, 44–47.

Instead, Petitioner's argument is that based on the combination of references, one of ordinary skill in the art would have understood that Wyeth's 50 mg/ml methotrexate solution could have been administered subcutaneously successfully, and would have been motivated to do so. *Id.* at 46. Petitioner provides evidence showing that subcutaneous and intramuscular administration are interchangeable ways of administering methotrexate (Ex. 1008, 91; Ex. 1023, 256; Ex. 1025, 256), and that the subcutaneous mode of administration is preferable as it is less painful and recommended to obtain the benefits of self-administration (Ex. 1008, 91; Ex. 1023, 256–57, 262). But this evidence at most shows that it would have been obvious to substitute subcutaneous administration in Wyeth in those instances where intramuscular administration is disclosed.

The dosages that Wyeth indicates for the treatment of inflammatory autoimmune diseases by intramuscular injection, however, are on the order of tens of milligrams. *See, e.g.*, Ex. 1021, 24 (stating that for psoriasis, a dosage of 30 mg/week should ordinarily not be exceeded). Thus, as we

discuss above, Petitioner has not established persuasively that Wyeth discloses a link between using its 1 gram vial, reconstituted to 50 mg/ml, and treating rheumatoid arthritis, whether it be via subcutaneous or intramuscular administration. That is, we do not find that the preponderance of the evidence shows that one of ordinary skill in the art would have understood Wyeth's 1 gram vial to be used for treating inflammatory autoimmune diseases requiring dosages on the order of tens of milligrams of methotrexate. *See supra* § II.E.2. Petitioner has not provided additional explanation—beyond its arguments on anticipation by Wyeth—as to why one of ordinary skill in the art would have found it obvious to use Wyeth's single-use 1 gram vial in connection with those dosage amounts. *See* Pet. 38–48.

"In an *inter partes* review, the burden of persuasion is on the petitioner to prove 'unpatentability by a preponderance of the evidence,' 35 U.S.C. § 316(e), and that burden never shifts to the patentee. 'Failure to prove the matter as required by the applicable standard means that the party with the burden of persuasion loses on that point—thus, if the fact trier of the issue is left uncertain, the party with the burden loses.'" *Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378–79 (Fed. Cir. 2015) (*quoting Licensing Corp. v. Videotek, Inc.*, 545 F.3d 1316, 1326–27 (Fed. Cir. 2008)). Based on the record before us, Petitioner has not shown by a preponderance of the evidence that claims 1–6, 11–13, 17, 18, and 22 would have been obvious over Wyeth, Brooks, Arthur, and Moitra.

G. Motion to Exclude

Patent Owner moves to exclude portions of the deposition testimony of Terri Shoemaker (Ex. 1040) and also Exhibits 1041–1045. Mot. to Exclude 1–8. We do not rely on any of Exhibits 1040–1045 in reaching this decision. Accordingly, we dismiss as moot Patent Owner's Motion to Exclude those exhibits.

III. CONCLUSION

For the foregoing reasons, we determine that Petitioner has failed to carry its burden of proving by a preponderance of the evidence that claims 1–22 of the '231 patent would have been unpatentable over the cited prior art. Also, Patent Owner's Motion to Exclude is dismissed as moot.

IV. ORDER

Accordingly, it is

ORDERED that claims 1–22 of the '231 patent have not been shown to be unpatentable by a preponderance of the evidence;

FURTHER ORDERED that Patent Owner's Motion to Exclude is dismissed as moot; and

FURTHER ORDERED that, because this is a final written decision, parties to the proceeding seeking judicial review of the decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

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