

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, TONI R. SCHEINER, and
ERICA A. FRANKLIN, *Administrative Patent Judges*.

BONILLA, *Administrative Patent Judge*.

DECISION
Granting Institution of *Inter Partes* Review
37 C.F.R. § 42.108

I. INTRODUCTION

On July 20, 2016, Koios Pharmaceuticals LLC (“Petitioner”) filed a Petition requesting an *inter partes* review of claims 1–22 of U.S. Patent No. 8,664,231 B2 (“the ’231 patent”) (Ex. 1001). Paper 1 (“Pet.”). medac Gesellschaft für klinische Spezialpräparate mbH (“Patent Owner”) filed a Preliminary Response to the Petition. Paper 11 (“Prelim. Resp.”).

Under 35 U.S.C. § 314(a), an *inter partes* review may not be instituted unless it is determined that there is “a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition.” Based on the information presented in the Petition and Preliminary Response, we are persuaded that there is a reasonable likelihood Petitioner would prevail with respect to the claims challenged in the Petition. Accordingly, we institute an *inter partes* review of claims 1–22 of the ’231 patent.

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-01498-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, filed March 2, 2015, which is currently pending at the Office. Paper 4, 2.

B. The '231 Patent

The '231 patent relates to a method for treating inflammatory autoimmune diseases, such as rheumatoid arthritis, juvenile rheumatoid arthritis, or 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 breast cancer and leukemia in children. *Id.* at 1:14–17, 1:24–27. Methotrexate also was used early on 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. Thus, antirheumatic therapy is referred to as “low-dosage methotrexate therapy.” *Id.* at 1:56–60. In this capacity, methotrexate is administered only once per

week, in dosages ranging from 5.0 to 30.0 mg per week in Germany, and up to 40.0 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 in the case of a certain dosage) 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 a 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 pain-free as possible, and in turn 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, in particular 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, solvent, inflammatory autoimmune diseases, self-administration, and the medicament being contained in an injection device for one or more applications, such as a pen injector, and in a storage container, such as a carpule.

D. Proposed Grounds of Unpatentability

Petitioner challenges the patentability of claims 1–22 of the '231 patent on the following grounds:

Reference(s)	Statutory Basis	Claims Challenged
Grint (Ex. 1003) ¹	§ 102(b)	1, 2, 4–6, 11–13, 17, and 22

¹ Grint et al., U.S. Patent No. 6,544,504 B1 (issued Apr. 8, 2003) (“Grint”) (Ex. 1003).

Reference(s)	Statutory Basis	Claims Challenged
Grint and Arthur (Ex. 1023) ² alone, or further in view of either Moitra (Ex. 1025) ³ or Insulin Admin. (Ex. 1015) ⁴	§ 103(a)	7–10, 14–16, and 19–21
Grint and Alsufyani (Ex. 1006) ⁵	§ 103(a)	18
Wyeth (Ex. 1021) ⁶	§ 102(b)	1–6, 11–13, 17, 18, and 22
Wyeth, Brooks (Ex. 1008), ⁷ and Arthur, further in view of Moitra or Insulin Admin.	§ 103(a)	1–22

² Valerie Arthur et al., *A Study of Parenteral Use of Methotrexate in Rheumatic Conditions*, 11 J. CLINICAL NURSING 256 (2002) (“Arthur”) (Ex. 1023). Petitioner also cites to Valerie Arthur et al., Letter to the Editor, 28 J. RHEUMATOLOGY 1, 212 (2001) (“Arthur 2001”) (Ex. 1024).

³ R.K. Moitra et al., *Caveats to the Use of Parenteral Methotrexate in the Treatment of Rheumatic Disease*, 44 RHEUMATOLOGY 256 (2005) (“Moitra”) (Ex. 1025).

⁴ Am. Diabetes Ass’n, *Insulin Administration*, 26 DIABETES CARE S121 (Supp. 1 2003) (“Insulin Admin.”) (Ex. 1015).

⁵ 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) (“Alsufyani”) (Ex. 1006).

⁶ WYETH PHARMACEUTICALS, METHOTREXATE SODIUM FOR INJECTION (2004) (“Wyeth”) (Ex. 1021). Petitioner also cites to Wyeth Pharmaceuticals, *Methotrexate Sodium Tablets, Methotrexate Sodium for Injection, Methotrexate LPF® Sodium (Methotrexate Sodium Injection) and Methotrexate Sodium Injection*, in PHYSICIANS’ DESK REFERENCE 3415 (57th ed. 2003) (“PDR for Wyeth”) (Ex. 1022).

⁷ Paul J. Brooks et al., *Pharmacokinetics of Methotrexate Administered by Intramuscular and Subcutaneous Injections in Patients with Rheumatoid Arthritis*, 33 ARTHRITIS & RHEUMATISM 91 (1990) (“Brooks”) (Ex. 1008).

Reference(s)	Statutory Basis	Claims Challenged
Hoekstra (Ex. 1004) ⁸ and Jørgensen (Ex. 1005) ⁹	§ 103(a)	1–6, 11–13, 17, and 22
Hoekstra, Jørgensen, and Arthur, in further view of Insulin Admin.	§ 103(a)	7–10, 14–16, and 19–21
Hoekstra, Jørgensen, and Alsufyani	§ 103(a)	18

Pet. 9–10. Petitioner also relies on the declarations of Donald Miller, Pharm.D. (Ex. 1033) and Michael H. Schiff, M.D. (Ex. 1034).

II. ANALYSIS

A. 35 U.S.C. § 325(d)

In the -1091 IPR and -649 IPR proceedings, we instituted *inter partes* reviews as to the same patent and claims challenged by Petitioner in this case. *Frontier Therapeutics, LLC v. medac Gesellschaft für klinische Spezialpräparate mbH*, Case IPR2016-00649, slip op. at 30–31 (PTAB Sept. 1, 2016) (Paper 10); *Antares Pharma, Inc. v. medac Gesellschaft für klinische Spezialpräparate mbH*, Case IPR2014-01091, slip op. at 24 (PTAB Jan. 6, 2015) (Paper 7). Several grounds that Petitioner asserts in this case are the same as those previously presented by the -1091 IPR and the -649 IPR petitioners. These include the challenges relying on (i) Grint under

⁸ Monique Hoekstra et al., *Bioavailability of Higher Dose Methotrexate Comparing Oral and Subcutaneous Administration in Patients with Rheumatoid Arthritis*, 31 J. RHEUMATOLOGY 645 (2004) (“Hoekstra”) (Ex. 1004).

⁹ Jan T. Jørgensen et al., *Pain Assessment of Subcutaneous Injections*, 30 ANNALS PHARMACOTHERAPY 729 (1996) (“Jørgensen”) (Ex. 1005).

§ 102(b) (*compare* Pet. 9, *with Frontier*, slip op. at 5, *and Antares*, slip op. at 5); (ii) Grint and Alsufyani under § 103(a) (*compare* Pet. 9, *with Frontier*, slip op. at 5, *and Antares*, slip op. at 5); (iii) Hoekstra and Jørgensen under § 103(a) (*compare* Pet. 10, *with Antares*, slip op. at 5); and (iv) Hoekstra, Jørgensen, and Alsufyani under § 103(a) (*compare* Pet. 10, *with Antares*, slip op. at 5). The -1091 IPR and -649 IPR petitioners did not assert any challenges involving the Arthur, Moitra, or Wyeth references. *See Frontier*, slip op. at 5–6; *Antares*, slip op. at 4–5.

After institution in each of the -1091 IPR and -649 IPR cases, the parties reached settlement agreements and jointly moved to terminate. -649 IPR, Paper 15; -1091 IPR, Paper 17. We granted the joint requests in both of these cases and terminated the proceedings without rendering final written decisions. -649 IPR, Paper 20; -1091 IPR, Paper 21. Petitioner states that it has no relationship with the petitioners in the -1091 IPR and -649 IPR cases. Pet. 3; Ex. 1035 ¶ 2.

Patent Owner argues that we should exercise our discretion and not institute trial in this case because this is the third IPR on the same claims of the '231 patent, and in filing when it did, Petitioner had the advantage of an institution decision and two preliminary responses by Patent Owner on the same claims challenged here. Prelim. Resp. 8–9, 12–14. Patent Owner further argues that the new prior art asserted in this case—Arthur, Moitra, and Wyeth—is redundant and cumulative of the art used in the -1091 IPR and -649 IPR. *Id.* at 9–12.

Petitioner, on the other hand, argues that we should reject Patent Owner's arguments because Petitioner is not in privity with, and has no relation to, either of the petitioners in the -1091 IPR and -649 IPR cases.

Pet. 61 (citing Ex. 1035 ¶ 2). Petitioner further asserts that in this case the Petition introduces new legal and factual arguments, prior art references, and expert declarations. *Id.* Also, Petitioner states that the Board has not previously adjudicated the merits of the arguments and references presented in the Petition. *Id.* at 62. At the time the Petition was filed, the -1091 IPR had been terminated by a private settlement before a final decision was entered (*id.*), and the -649 IPR was later terminated in this manner as well.

Under 35 U.S.C. § 325(d), in determining whether to institute *inter partes* review, we “may take into account whether, and reject the petition or request because, the same or substantially the same prior art or arguments previously were presented to the Office.” 35 U.S.C. § 325(d). We decline to exercise our discretion in this case to deny institution. In doing so, we accept Petitioner’s representation that it is not in privity with, and has no relationship with, either of the petitioners in the -1091 IPR and -649 IPR cases. Pet. 3, 61; Ex. 1035 ¶ 2. Furthermore, the -1091 IPR and -649 IPR were terminated, upon the submission of joint requests to which Patent Owner was a party, before the merits of those proceedings could be resolved in final written decisions. We have previously declined to exercise our discretion under § 325(d) to deny institution in similar circumstances. *See, e.g., Square, Inc. v. Protegrity Corp.*, Case CBM2014-00182, slip op. at 7–8 (PTAB Mar. 5, 2015) (Paper 16) (declining to exercise discretion to deny petition (filed on August 29, 2014), where previously-filed petition based on the same prior art and substantially similar arguments was filed by a different petitioner and the first proceeding (instituted on April 15, 2014) settled before issuance of a final written decision).

Additionally, although Patent Owner argues that Arthur, Moitra, and Wyeth are cumulative of the art used in the -1091 IPR and -649 IPR cases, Patent Owner also acknowledges that unlike analogous prior art references applied in the -1091 IPR and -649 IPR, Wyeth contains a disclosure regarding subcutaneous administration. Prelim. Resp. 10–11.

“[S]ubcutaneously administering” the medicament is a material limitation in the ’231 patent’s claims. Accordingly, we do not view Wyeth as being “substantially the same prior art” as asserted in the -1091 IPR and -649 IPR proceedings.

B. Petitioner’s Declarations

1. Dr. Miller

Patent Owner argues that the expert opinions expressed by Dr. Miller should be given no weight. Prelim. Resp. 14–16. Patent Owner contends that Dr. Miller lacks adequate clinical experience as a pharmacist in preparing methotrexate and treating inflammatory autoimmune diseases with methotrexate. *Id.* at 14–15. Patent Owner also finds part of Dr. Miller’s testimony to be flawed and illogical, and elsewhere inconsistent with Dr. Schiff’s testimony. *Id.* at 15–16 (citing Ex. 1033 ¶¶ 9, 71; Ex. 1034 ¶ 123).

We have considered Patent Owner’s arguments, but for the purpose of institution, on the limited record before us, we are not persuaded that Dr. Miller lacks credibility to the extent that his declaration should be given no weight whatsoever. For instance, Dr. Miller testifies that he has co-authored articles on the subject of treating rheumatoid arthritis with methotrexate and lectured on the topic of drugs for managing rheumatoid arthritis. Ex. 1033 ¶ 10. Dr. Miller’s credentials provide sufficient reason to consider his

declaration at this stage of the proceeding. And regardless, we have not found it necessary to rely on the specific portions of Dr. Miller's testimony that Patent Owner objects to (i.e., Ex. 1033 ¶¶ 9, 71) in determining whether to institute *inter partes* review.

2. Dr. Schiff

Patent Owner likewise argues that Dr. Schiff's opinions should not be given weight. Prelim. Resp. 17–19. Patent Owner identifies a prior consulting agreement that Dr. Schiff had with medac Pharma, Inc., under which Dr. Schiff received confidential information relating to the '231 patent, and Patent Owner states that Dr. Schiff's acting as an expert here is inconsistent with that consulting agreement. *Id.* at 17 (citing Ex. 2007 ¶ 4.1; Ex. 2008; Ex. 2011 ¶¶ 5–6). Patent Owner also argues that Dr. Schiff's testimony that the concentrated methotrexate solutions claimed in the '231 patent were known and employed by physicians before the priority date of the '231 patent is unsupported by evidence and inconsistent with Dr. Schiff's own clinical practice before 2006—namely, that he treated patients with autoimmune diseases with multiple subcutaneous injections of methotrexate having concentrations of 25 mg/ml as opposed to prescribing a more concentrated dose. *Id.* at 17–19.

Whether Dr. Schiff breached his consulting agreement is not at issue here. Rather, Dr. Schiff's testimony is relevant to the extent it addresses the understanding of one of ordinary skill in the art at the time of the invention. Patent Owner points to no authority stating that a consultant who received confidential information concerning an invention may not later present expert testimony addressing the understanding of one of ordinary skill in the art at the time of the invention. *See id.* at 17. In any event, on this

preliminary record, there is no indication that Dr. Schiff is relying on any of Patent Owner's confidential information and we have not considered or relied on the redacted portions of Dr. Schiff's testimony in this decision.

We acknowledge Patent Owner's other arguments regarding Dr. Schiff's declaration, including asserted inconsistencies between Dr. Schiff's testimony and his clinical practice, and have taken into account Patent Owner's arguments in determining the weight to give Dr. Schiff's testimony. We further note that in instituting *inter partes* review, we have relied on Dr. Schiff's testimony regarding his understanding of the express disclosures of the prior art, as opposed to Dr. Schiff's testimony regarding the practice of physicians at the relevant time to the extent this latter testimony is not supported by additional evidence.

C. Claim Construction

In an *inter partes* review, the Board interprets claim terms in an unexpired patent according to the broadest reasonable construction in light of the specification of the patent in which they appear. *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144–46 (2016); 37 C.F.R. § 42.100(b). Under that standard, we give claim terms their ordinary and customary meaning, as would be understood by one of ordinary skill in the art, when read in view of the specification. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1256–57 (Fed. Cir. 2007). “[O]nly those terms need be construed that are in controversy, and only to the extent necessary to resolve the controversy.” *Vivid Techs., Inc. v. Am. Sci. & Eng’g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999).

Petitioner discusses the meaning of five claim terms, explaining that those terms are “presumed to take on their ordinary and customary meaning

that they would have to one of ordinary skill in the art.” Pet. 10–11. For example, Petitioner asserts that “subcutaneously” means “[u]nder the skin.” *Id.* at 10. Patent Owner does not propose different constructions for the claim terms, but clarifies that “subcutaneously” is distinct from, and does not include, “intramuscular” or “intravenous,” despite the fact that all three involve administration “literally” under the skin. Prelim. Resp. 20–21.

We agree with Patent Owner that subcutaneously is a route of administration that is distinct from intramuscular (in a muscle) or intravenous (in a vein). 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 parenterally. In particular, the medicaments are administered by intravenous, intramuscular or subcutaneous injection.”); *id.* at 5:32–35.

In view of our analysis, we determine that construction of the remaining claim terms is not necessary for purposes of this Decision.

D. 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 opposes Petitioner’s assertion. Prelim. Resp. 21–23.

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. The interleukin-10 and methotrexate may be administered either together in a single pharmaceutical composition or separately. *Id.* at 3:20–21. The methotrexate may be administered parenterally, including subcutaneously. *Id.* at 5:64, 7:56–59, 8:1–2. Grint

states 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.

2. Analysis

Independent claim 1 recites “subcutaneously administering . . . a medicament comprising methotrexate . . . at a concentration of more than 30 mg/ml.” In its arguments and claim charts, Petitioner points to where Grint discloses every limitation of claim 1, as well as the limitations of the other challenged claims. Pet. 12–22.

Claim 1’s limitation of “more than 30 mg/ml” overlaps the range of methotrexate concentration (“about 0.1 to about 40 mg/ml”) disclosed in Grint. *See id.* at 13–14. Nonetheless, Petitioner contends that one of ordinary skill in the art would have understood Grint to disclose subcutaneous administration of methotrexate in the claimed concentration for the treatment of inflammatory autoimmune diseases. *Id.* at 16–17 (citing Ex. 1034 ¶¶ 49–53). Petitioner cites to Dr. Schiff’s testimony, which in turn relies on Grint’s disclosure that “[m]ethotrexate is compounded for convenient and effective administration in effective amounts” preferably ranging from 1 to 35 mg (Ex. 1003, 6:60–65), to conclude:

Given those disclosures, a skilled artisan would thus 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 (quoting Ex. 1003, 6:60–63).

In response, Patent Owner argues that Petitioner has not shown that there is “no reasonable difference in how the invention operates” over Grint’s 0.1–40 mg/ml range, and in fact, there is a difference in how the invention operates over Grint’s range. Prelim. Resp. 22 (quoting *Ineos USA LLC v. Berry Plastics Corp.*, 783 F.3d 865, 869 (Fed. Cir. 2015)). Patent Owner states that “even if it is (incorrectly) assumed that the disclosures of Grint regarding dosages and concentrations apply equally to all methods of administration,” then Grint would indicate injection volumes of from 0.0025 ml to 4,000 ml. *Id.* According to Patent Owner, however, “Petitioner itself admits that volumes greater than 1 ml are not appropriate for subcutaneous administration due to the pain caused.” *Id.*

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.” *Ineos*, 783 F.3d at 869. In other words, to avoid anticipation, it is important to establish the criticality of a claimed range to the operability of the claimed invention; if a person of ordinary skill in the art would expect that the claimed invention would operate differently, or not at all, outside of the claimed range, then the claimed range is critical. *Id.* at 869–71. The inquiry must consider “[h]ow one of ordinary skill in the art would understand the scope of the disclosure

or, stated differently, how one of ordinary skill in the art would understand the relative size of a genus or species in a particular technology.” *OSRAM Sylvania, Inc. v. Am. Induction Techs., Inc.*, 701 F.3d 698, 706 (Fed. Cir. 2012).

Here, Petitioner’s assertion that “a skilled artisan would have understood Grint to disclose subcutaneous administration of [methotrexate] in concentrations greater than 30 mg/ml for the treatment of inflammatory autoimmune diseases” is supported by Dr. Schiff’s testimony and reasoning. Pet. 16–17; Ex. 1034 ¶¶ 49–52. On this record, therefore, we cannot conclude that “one of ordinary skill would not have recognized [more than 30 mg/ml] as an acceptable value for the range provided in the prior art.” *OSRAM*, 701 F.3d at 705–06.

Furthermore, at this stage, there is insufficient evidence that the claimed concentration range is critical to the operability of the claimed invention. At most, the ’231 patent identifies higher concentration ranges that “can be expected” to provide a “positive impact” on patient compliance. Ex. 1001, 5:22–23. The ’231 patent provides no further evidence confirming this expectation, including whether the positive impact is significant enough such that the claimed method would be considered to operate differently outside of the claimed concentration range. On the contrary, the ’231 patent recognizes that the known methotrexate solutions in ready-made syringes of the prior art already have had a positive impact on patient compliance. *Id.* at 4:65–5:1.

Moreover, the additional advantages to patient compliance disclosed in the ’231 patent are a result of smaller injection *volumes*. *See id.* at 2:45–52 (disclosing as problematic having to inject a relatively large amount of

solution, e.g., up to 3 ml); *id.* at 5:5–23 (comparing the injection of a 3 ml volume, which is described as difficult to convey to a patient, with a 0.6 ml injection that can be expected to have a positive impact on patient compliance). Accordingly, under the '231 patent's theory, there would be no difference in the difficulty of conveying an injection to a patient over Grint's concentration range of about 0.1 to about 40 mg/ml where the injections are all provided at the same volume, for example in 1 ml volumes.

For this reason, Patent Owner's argument that Grint could potentially indicate injection volumes of from 0.0025 ml to 4,000 ml is not persuasive. First, Patent Owner admits that its volume calculations are based on an incorrect assumption. Prelim. Resp. 22 (“[E]ven if it is (incorrectly) assumed that the disclosures of Grint regarding dosages and concentrations apply equally to all methods of administration, the smallest volume . . . would be 0.0025 ml, and the largest volume . . . would be 4,000 ml.”); *see also* Ex. 1033 ¶ 46 (“[A] skilled artisan would have further understood that it would be inconvenient and ineffective to use a 40 mg/ml concentration to administer 1 mg of [methotrexate], as this would require a 0.025 ml solution, which cannot be accurately drawn and administered.”). Second, another set of calculations may hold the volume constant (e.g., at 1 ml) across Grint's concentration range so that the concentration (and number of injections, if necessary) are varied depending on the size of the total dosage being administered.

We recognize that there is less overlap between Grint's concentration range and the ranges set forth in the dependent claims, specifically claim 2 (reciting that the methotrexate concentration is “more than 30 mg/ml to 100 mg/ml”) and claim 22 (reciting that the methotrexate concentration is “from

40 mg/ml to 80 mg/ml”). However, given the lack of evidence of criticality of the claimed range on the current record, we find that at this stage there is a reasonable likelihood that Petitioner would succeed in its challenge to the dependent claims identified in the Petition as being anticipated by Grint as well. *See Ineos*, 783 F.3d at 869 (finding that the district court erred in concluding that a prior art reference disclosed particular points within a range because “the disclosure of a range . . . does not constitute a specific disclosure of the endpoints of that range” but nevertheless affirming the district court’s anticipation holding because the claimed range was not critical to the operability of the invention (quoting *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 1000 (Fed. Cir. 2006))).

Based on the information presented at this stage of the proceeding, we are persuaded that Petitioner has shown a reasonable likelihood of establishing that each limitation of claims 1, 2, 4–6, 11–13, 17, and 22 is disclosed by Grint. Pet. 12–22.

E. Obviousness over Grint and Arthur Alone, or Further in View of Either Moitra or Insulin Admin.

Petitioner asserts that dependent claims 7–10, 14–16, and 19–21 of the ’231 patent are obvious over Grint and Arthur alone, or further in view of either Moitra or Insulin Admin. Pet. 22–28.¹⁰ Patent Owner opposes Petitioner’s assertion. Prelim. Resp. 23–26.

¹⁰ Petitioner cites to Arthur 2001 (Ex. 1024) as additional evidence. Pet. 9–10, 26–27. Petitioner merely states that Arthur’s findings are reported in summary format in Arthur 2001. *Id.* at 26–27. The relevance of Arthur 2001 is unclear as the Petition does not cite Arthur 2001 as disclosing any claim limitations or as supportive of a reason to combine. Accordingly, we do not give Arthur 2001 any weight. *See* 37 C.F.R. § 42.104(b)(5) (“The Board may exclude or give no weight to the evidence where a party has

1. *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, at 256. In the study, patients were taught to self-administer methotrexate subcutaneously and were then discharged to perform this task at home. *Id.* The patients were provided three pre-filled syringes and subcutaneously administered their methotrexate at home for three consecutive weeks. *Id.* at 259. The study concludes that there is no difference in the safety and efficacy given by either parenteral route. *Id.* at 256. The study recommends that patients receiving methotrexate intramuscularly should be switched to the subcutaneous route and, in the future, parenteral methotrexate should be prescribed by the subcutaneously instead of the intramuscularly. *Id.* at 262.

The authors further recommend that patients who are able should self-administer their injections at home. *Id.* According to Arthur, self-administration reduced hospital visits, was more convenient for patients, and improved patient satisfaction. *Id.* at 257.

2. *Moitra*

Moitra describes methotrexate as one of the most widely prescribed anti-rheumatic drugs. Ex. 1025, at 256. Moitra states that there are no significant differences between methotrexate administered subcutaneously and intramuscularly, making the two routes interchangeable. *Id.* In Moitra's study, of 91 patients using subcutaneous injections, 77 had been taught to self-inject. *Id.* Nevertheless, Moitra explains that parenteral methotrexate is

failed to state its relevance or to identify specific portions of the evidence that support the challenge.”).

more expensive than the oral form, and therefore all reasonable steps should be taken to ensure that patients are given an adequate trial of the oral drug before switching to the parenteral form. *Id.* Accordingly, Moitra concludes that before switching from oral to parenteral methotrexate, dose escalation and simple symptom control measures to deal with common side effects should be attempted. *Id.* at 257.

3. *Insulin Admin.*

Insulin Admin. addresses issues regarding the use of conventional insulin administration in the self-care of an individual with diabetes. Ex. 1015, at S121. The article explains that several pen-like devices and insulin containing cartridges are available that deliver insulin subcutaneously through a needle. *Id.* at S123. In many patients, including those using multiple daily injection regimens, those devices have been shown to improve accuracy of insulin administration and/or adherence. *Id.* According to the article, low-dose pens that deliver insulin in half-unit increments are also available. *Id.* The article also explains that certain individuals, such as those dependent on others for drawing their insulin, may benefit from using prefilled syringes. *Id.*

4. *Analysis*

Claim 7 requires the medicament comprising methotrexate of independent claim 1 to be “present in a form suitable for patient self-administration.” Claims 8 and 9 specifically require the medicament to be contained in an injection device for a single application, while claim 10 further requires the injection device to be a ready-made syringe, and claim 20 requires the injection device to be a pen injector. Claims 14–16, 19, and

21 recite additional limitations relating to the medication storage, the injection device and the dosages per application administered by the device.

In its arguments and claim charts, Petitioner points to where Grint, Arthur, Moitra, and Insulin Admin. disclose the limitations of claims 7–10, 14–16, and 19–21. Pet. 22–28. Petitioner argues that it would have been obvious to combine Grint and Arthur so that the methotrexate solution could be suitable for self-administration, as Arthur teaches the benefits of self-administration. *Id.* at 26–27 (citing Ex. 1023, at 256–57). Petitioner also points to Moitra’s study in which 77 out of 91 patients had been taught to self-inject methotrexate successfully as further evidence that one of ordinary skill in the art would have had a reason to combine Grint and Arthur with an expectation of success. *Id.* at 27 (citing Ex. 1025, at 256). Petitioner further proposes combining the teachings of Grint and Arthur with Insulin Admin.’s pen-like devices based on Insulin Admin.’s teaching that these devices have been demonstrated to improve accuracy of insulin administration and/or adherence. *Id.* at 27–28 (citing Ex. 1015, at S123).

Patent Owner argues that Petitioner has not clearly identified its proposed combinations and cites to previous cases where the Board declined institution of grounds that lacked clarity. Prelim. Resp. 23–25. Patent Owner also argues that the reasons to combine prior art teachings as set forth in the Petition are conclusory and insufficient, citing as an example to the Petition’s treatment of Insulin Admin. *Id.* at 25–26. And Patent Owner further states that Petitioner fails to address why Insulin Admin., Moitra, and Arthur do not teach away from the proposed combinations. *Id.* at 26.

In a footnote, Patent Owner also contends that Petitioner has not met its burden of establishing that Arthur, Moitra, and Insulin Admin. qualify as printed publications and authenticating these references. *Id.* at 23 n.3.

a. Clarity of Petition

We are persuaded that Petitioner sufficiently identifies in its claim charts which portions of the prior art references Petitioner relies upon as disclosing each of the elements of challenged claims 7–10, 14–16, and 19–21. Pet. 23–25. As discussed above, Petitioner sets forth an anticipation ground based on Grint in relation to challenged independent claim 1, upon which all other challenged claims depend. We understand Petitioner’s position to be that Grint does not disclose the limitations specifically recited in dependent claims 7–10, 14–16, and 19–21, as set out in the claim chart for this obviousness ground. *Id.*

In arguing that it would be obvious to combine the references, the Petition quotes explicit teachings from those references that would provide one of ordinary skill in the art with a reason to combine Grint with Arthur, Moitra, and Insulin Admin. Specifically, Petitioner quotes Arthur’s teaching that “[s]elf-administration reduced hospital visits, was more convenient for patients and improved patient satisfaction”; Moitra’s teaching that out of 91 patients, “77 patients ‘had successfully been taught to self-inject’”; and Insulin Admin.’s teaching that its “devices have been demonstrated to improve accuracy of insulin administration and/or adherence.” *Id.* at 26–28 (quoting Ex. 1023, at 256–57; Ex. 1025, at 256; Ex. 1015, at S123).

Also, to further support the combination of Insulin Admin. with Grint, Petitioner cites Dr. Miller’s declaration, which likewise relies on Insulin Admin.’s disclosures in articulating a reason to combine. *Id.* at 28 (citing

Ex. 1033 ¶ 60); *see also* Ex. 1033 ¶ 60 (“[A] person of skill in the art would have wanted to use the higher concentration of [methotrexate] solution, such as that disclosed in Grint, with an injection device such as the prefilled syringe or ‘pen-like’ injector disclosed in Insulin Admin., as it would promote self-administration, improve patient compliance, and be more convenient for the patient, physician, and treating clinic.”).

Accordingly, at this stage, we find that the Petition has identified where each of the elements of the challenged claims are disclosed in the prior art and further identified specific teachings from the prior art references that support why one of ordinary skill in the art would have a reason to combine the references such that there is a reasonable likelihood that Petitioner will succeed on its obviousness challenge.

b. Teaching Away

At this preliminary stage, we do not view Arthur, Moitra, and Insulin Admin., when each of those references is read as a whole, as teaching away from the proposed combinations. “A statement that a particular combination is not a preferred embodiment does not teach away absent clear discouragement of that combination.” *Syntex (U.S.A.) LLC v. Apotex, Inc.*, 407 F.3d 1371, 1380 (Fed. Cir. 2005).

Patent Owner cites to a portion of Arthur discussing injection site reactions (Prelim. Resp. 26), which were reported by a minority of patients in response to a survey designed to discover problems with self-administration (Ex. 1023, at 261). The Arthur study, however, describes those problems as either not attributable to the injection itself, less severe when compared to intramuscular injection, or non-recurring. *See id.* at 261. Importantly, there is no clear discouragement of subcutaneous self-

administration in Arthur. On the contrary, Arthur expressly recommends it. *Id.* at 262.

In relation to Moitra, Patent Owner points to a statement that “conclusions cannot be drawn due to the retrospective nature of this analysis and the lack of an appropriate control.” Prelim. Resp. 26 (quoting Ex. 1025, at 257). In the same sentence, however, Moitra states that “[p]arenterally administered [methotrexate] is generally better tolerated and there is a suggestion that it is more efficacious.” Ex. 1025, at 257. Moitra is not clearly discouraging parenteral administration *per se*, but rather cautioning that before moving from oral to parenteral administration, one should attempt dose escalation and symptom control measures. *Id.*

Notably, Patent Owner does not cite to any passage from Insulin Admin. that allegedly teaches away. *See* Prelim. Resp. 26.

c. Printed Publications / Authentication

On this record and at this stage of the proceeding, we find that Petitioner has made a threshold showing that Arthur, Moitra, and Insulin Admin. are printed publications. Each article, on its face, appears to be published in a periodical having a format that is consistent with published articles in technical journals. *See Oracle Am., Inc. v. Realtime Data LLC*, Case IPR2016-00374, slip op. at 16–17 (PTAB June 27, 2016). Additionally, although Patent Owner also cites to cases involving questions of authentication, these cases are not applicable here, in the context of self-authenticating periodicals. *See* Fed. R. Evid. 902(6).

F. Obviousness over Grint in view of Alsufyani

Petitioner asserts that dependent claim 18 of the '231 patent is obvious over Grint in view of Alsufyani. Pet. 28–30. Patent Owner opposes Petitioner's assertion. Prelim. Resp. 26 n.4.

1. Alsufyani

Alsufyani is a journal article discussing subcutaneous administration of methotrexate as a treatment for juvenile idiopathic arthritis. Ex. 1006, at 179. In particular, Alsufyani describes a study showing that the majority of children with juvenile idiopathic arthritis who have experienced an inadequate response to oral methotrexate, or who have developed toxicity to oral methotrexate, will gain a substantial benefit of an improved response without increased toxicity after switching to subcutaneous methotrexate. *Id.* at 180–81. Alsufyani specifically concludes that “the use of [subcutaneous methotrexate] has a high likelihood of success with more than 70% of patients achieving clinically significant improvement, without clinically significant toxicity.” *Id.* at 179.

2. Analysis

Claim 18 recites “juvenile rheumatoid arthritis” as the autoimmune disease treated by the method of independent claim 1. Petitioner contends that Alsufyani teaches that subcutaneous methotrexate administration is effective for the treatment of juvenile rheumatoid arthritis. Pet. 29. Relying on Dr. Schiff's declaration, Petitioner argues that one of ordinary skill in the art would have a reasonable expectation of success in applying the teachings of Grint to the treatment of juvenile idiopathic arthritis using similar dosages of methotrexate, as disclosed in Alsufyani. *Id.* at 29–30 (citing Ex. 1034 ¶¶ 70–71).

Patent Owner contends that Petitioner provides no more than conclusory arguments as to why one of ordinary skill in the art would have combined Alsufyani with Grint and such conclusory assertions are insufficient to establish obviousness. Prelim. Resp. 26 n.4. Patent Owner also argues that Petitioner has not met its burden of establishing that Alsufyani qualifies as a printed publication. *Id.* at 23 n.3.

On the record before us at this stage, Petitioner sufficiently establishes that an ordinary artisan would have had a reason to use subcutaneous methotrexate treatment in connection with juvenile idiopathic arthritis, given Alsufyani's findings of a high likelihood of success and clinically significant improvement, without clinically significant toxicity. Pet. 28–29 (quoting Ex. 1006, at 179). The Petition cites Dr. Schiff's declaration, which also relies on the teachings of Alsufyani, in support. *Id.* at 29 (citing Ex. 1034 ¶¶ 70–71); *see also* Ex. 1034 ¶ 71 (“[A] person of ordinary skill in the art would have expected to successfully treat [juvenile rheumatoid arthritis] by subcutaneously administering the ≥ 30 mg/ml [methotrexate] solution of Grint because Alsufyani specially discloses that subcutaneous administration of [methotrexate] has a high likelihood of success in treating [juvenile rheumatoid arthritis].”).

We further find that Petitioner has made a threshold showing that Alsufyani is a printed publication for the same reasons discussed above, in regard to Arthur, Moitra, and Insulin Admin.

G. Anticipation by Wyeth

Petitioner asserts that Wyeth anticipates claims 1–6, 11–13, 17, 18, and 22 of the '231 patent. Pet. 30–38. Petitioner alleges that “[e]ach of the relevant disclosures in Wyeth is also found in the PDR for Wyeth.” *Id.* at 31

n.6. Patent Owner opposes Petitioner's assertion of anticipation by Wyeth. Prelim. Resp. 27–30.

1. Wyeth

Wyeth is an FDA-approved printed package insert for an injectable methotrexate product. *See* Pet. 30; Ex. 1021, at 1. Specifically, Wyeth discloses “Methotrexate Sodium for Injection products . . . given by the intramuscular, intravenous, intra-arterial or intrathecal route.” Ex. 1021, at 3. Wyeth's injection products are available in 20 mg and 1 gram vials. *Id.* at 3, 24–25. Additionally, Wyeth also provides methotrexate sodium tablets for oral administration. *Id.* at 23–24.

Wyeth sets forth dosage and administration schedules for treating adult rheumatoid arthritis, polyarticular-course juvenile rheumatoid arthritis, and psoriasis. *Id.* Recommended weekly, single doses are 7.5 mg for adult rheumatoid arthritis administered orally, and 10 to 25 mg for psoriasis administered orally, intramuscularly, or intravenously. *Id.* Wyeth also provides an option of divided oral dosages of 2.5 mg at 12-hour intervals for each of these conditions. *Id.*

As for polyarticular-course juvenile rheumatoid arthritis, Wyeth initially states that “[t]he recommended starting dose is 10 mg/m² given once weekly,” without mentioning any particular administration route. *Id.* at 23. Wyeth then goes on to mention that for either adult or juvenile rheumatoid arthritis, dosages may be adjusted gradually to achieve an optimal response. *Id.* At higher doses, Wyeth states: “Experience does suggest, however, that children receiving 20 to 30 mg/m²/wk . . . may have better absorption and fewer gastrointestinal side effects if methotrexate is administered either intramuscularly or subcutaneously.” *Id.*

Wyeth instructs to reconstitute its injection products immediately prior to use and 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 25. The 20 mg and 1 g vials are each for single use only. *Id.* at 3, 26

2. *PDR for Wyeth*

The PDR for Wyeth is an excerpt from the *Physicians' Desk Reference*, a book that compiles drug product information, i.e., manufacturer package inserts, used primarily as a reference for physicians. The PDR for Wyeth includes product information for methotrexate drugs, including methotrexate sodium tablets and methotrexate sodium for injection. Ex. 1022, at 3415, col. 3.

Relevant disclosures in the PDR for Wyeth are substantially the same as those in Wyeth. For example, the PDR for Wyeth discloses the same product, “Methotrexate Sodium for Injection . . . available in 20 mg and 1 gram vials,” given by the same administration routes (*id.* at 3416, col. 2); the same dosage and administration schedules for treating adult rheumatoid arthritis, polyarticular-course juvenile rheumatoid arthritis, and psoriasis (*id.* at 3419, col. 3 to 3420, col. 1); the same statement that children receiving the higher doses may have better absorption and fewer gastrointestinal side effects if methotrexate is administered either intramuscularly or subcutaneously (*id.* at 3420, col. 1); and the same reconstitution instructions (*id.*).

3. *Analysis*

In its arguments and claim charts, Petitioner points to where Wyeth or PDR for Wyeth discloses every limitation of claim 1, as well as the

limitations of the other challenged claims. Pet. 30–38. For example, Petitioner points to where Wyeth teaches administering methotrexate to treat psoriasis and “Rheumatoid Arthritis including Polyarticular-Course Juvenile Rheumatoid Arthritis,” as well as administering the drug subcutaneously, and reconstituting the methotrexate product to a concentration of 50 mg/ml. *Id.* at 31–32 (citing Ex. 1021, at 7, 23, 24; Ex. 1034 ¶¶ 74–76, 78, 82).

In response, Patent Owner argues that Petitioner relies on two separate references (Wyeth and PDR for Wyeth) for its anticipation argument, yet Petitioner does not argue why it would be obvious to combine them, or if considered anticipatory references, why one reference is not cumulative of the other. Prelim. Resp. 27. Patent Owner further views Wyeth’s disclosure of subcutaneous administration as “a mere anecdote, which is presented as an aside.” *Id.* at 28. Patent Owner also contends that Petitioner has not addressed why one of ordinary skill in the art would override the explicit instructions for oral administration in the treatment of rheumatoid arthritis. *Id.* In addition, Patent Owner quotes Wyeth’s disclosures stating that experience only “suggest[s]” that intramuscular or subcutaneous administration “may” have better results, and there are “too few published data” regarding dosages over 20 mg/m²/wk given to children. *Id.* (quoting Ex. 1021, at 23; Ex. 1022, at 3420, col. 1). Patent Owner questions why in the context of these disclosures, Wyeth should be interpreted as instructions to use any Wyeth product subcutaneously and at Wyeth’s disclosed concentrations. *Id.*

We do not understand Petitioner to be asserting that the challenged claims are anticipated based on a combination of Wyeth and PDR for Wyeth, but rather, given that each of the relevant disclosures in Wyeth are

also found in the PDR for Wyeth (Pet. 31 n.6), the challenged claims are either anticipated by Wyeth alone or by PDR for Wyeth alone. Because Petitioner does not make any meaningful distinction between Wyeth and PDR for Wyeth, we consider whether to institute *inter partes* review in relation to this ground only based on Wyeth, which is the reference primarily relied upon by Petitioner.

Patent Owner characterizes Wyeth's disclosure of subcutaneous administration as a "mere anecdote" and an "aside," and focuses on qualifying words such as "suggest[s]" and "may." Prelim. Resp. 27–28. There is no dispute, however, that Grint expressly discloses, as a known treatment practice, subcutaneous administration in the context of children receiving treatment for polyarticular-course juvenile rheumatoid arthritis. *See* Ex. 1021, at 23. In addition, Wyeth refers to "too few published data" in the context of a connection between dosage amounts and toxicity, not concentrations or the benefits of subcutaneous administration. *Id.*; Prelim. Resp. 28 (referring to the "too few published data").

Patent Owner argues that Wyeth gives explicit instructions to administer methotrexate orally. This is not always the case, however. Wyeth instructs administering methotrexate orally for the starting dose treatment of adult rheumatoid arthritis and psoriasis. *See* Ex. 1021, at 23–24. For the separate condition of polyarticular-course juvenile rheumatoid arthritis, Wyeth is silent on the mode of administration for the starting dose. *Id.* Wyeth states, however, that "[e]xperience does suggest . . . better absorption and fewer gastrointestinal side effects if methotrexate is administered either intramuscularly or subcutaneously" when treating polyarticular-course juvenile rheumatoid arthritis at higher doses. *Id.*

Accordingly, without persuasive evidence on the record that supports Patent owner’s position, we find that there is a reasonable likelihood that Petitioner would show that one of ordinary skill in the art would at once envisage using either of Wyeth’s two injection products (one of which is reconstituted to 50 mg/ml) as applicable for the subcutaneous administration disclosed in Wyeth. *See Kennametal, Inc. v. Ingersoll Cutting Tool Co.*, 780 F.3d 1376, 1381 (Fed. Cir. 2015) (“[A] reference can anticipate a claim even if it ‘d[oes] 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.” (second alteration in original) (quoting *In re Petering*, 301 F.2d 676, 681 (CCPA 1962))).

H. Obviousness over Wyeth in View of Brooks and Arthur, Further in View of Moitra or Insulin Admin.

Petitioner asserts that claims 1–22 of the ’231 patent are obvious over Wyeth in view of Brooks and Arthur, further in view of Moitra or Insulin Admin. Pet. 38–48.¹¹ Patent Owner opposes Petitioner’s assertion. Prelim. Resp. 30–32.

1. Brooks

Brooks is a journal article comparing the pharmacokinetics of methotrexate after intramuscular and subcutaneous injections in patients with rheumatoid arthritis. Ex. 1008, at 91. Brooks explains that statistical analysis of its study results “suggests that the pharmacokinetic parameters

¹¹ Once again, Petitioner cites to Arthur 2001 (Ex. 1024) as additional evidence. Pet. 10. The Petition, however, does not cite or discuss Arthur 2001 in the explanation of this ground. *See id.* at 38–48. Accordingly, the relevance of Arthur 2001 is unclear and, as above, we do not give Arthur 2001 any weight. *See* 37 C.F.R. § 42.104(b)(5); *supra* note 10.

are similar for these 2 routes of administration.” *Id.* at 93. 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.* Brooks also reports that most patients found the subcutaneous injection less painful than the intramuscular injection. *Id.*

2. Analysis

a. Claims 1–6, 11–13, 17, 18, and 22

In its arguments and claim charts, Petitioner points to where Wyeth, PDR for Wyeth, Brooks, Arthur, and Moitra, disclose the limitations of claims 1–6, 11–13, 17, 18, and 22. Pet. 22–28. Petitioner relies on an embodiment from Wyeth that discloses intramuscular injection and then contends that Brooks, Arthur, and Moitra each provide evidence that in treating rheumatic diseases, subcutaneous injections are interchangeable with, or more advantageous than, intramuscular injections. *Id.* at 38–40, 45–46.

Patent Owner responds, as above, by stating that the Petition lacks clarity. According to Patent Owner, the Petition is unclear as to whether it is using Wyeth and PDR for Wyeth in combination or individually and Petitioner gives no reason for why one would combine the two references. Prelim. Resp. 30, 32. Patent Owner states that the Petition is further unclear as to which limitations it contends are missing from Wyeth and/or PDR for Wyeth and what disclosures of the secondary references Petitioner is proposing to combine. *Id.* at 31. Patent Owner also contends that Petitioner’s arguments in support of combining all of the references are

insufficient because Petitioner provides no arguments at all for combining Moitra and Insulin Admin. with Wyeth or PDR for Wyeth, and Petitioner only provides conclusory arguments in support of combining Wyeth and PDR for Wyeth with Brooks or Arthur. *Id.* at 31–32.

Regarding Petitioner’s dual use of Wyeth and PDR for Wyeth, as discussed above, Petitioner does not make any meaningful distinction between Wyeth and PDR for Wyeth. Thus, we consider whether to institute *inter partes* review in relation to this ground based only on Wyeth, which is the reference Petitioner primarily relies on.

We are persuaded that Petitioner sufficiently identifies in its claim charts which portions of the prior art references Petitioner relies upon as disclosing each of the elements of the challenged claims. Pet. 38–43. For example, we understand Petitioner to be relying on either of Brooks, Moitra, or Arthur—not Wyeth—to meet the “subcutaneously administering” claim limitation for purposes of this obviousness challenge. *Id.* at 39–40; *see also id.* at 45 (relying on Wyeth’s disclosure of intramuscular injection).

In addition, we are persuaded, based on the record before us, that Petitioner sets forth a sufficient reason to combine Wyeth with Brooks, Moitra, and Arthur in regard to claim 1. In its analysis section, Petitioner quotes from express disclosures in Brooks, Moitra, and Arthur teaching that subcutaneous and intramuscular injections are interchangeable routes of methotrexate administration. *Id.* at 45 (quoting Ex. 1008, at 91; Ex. 1023, at 256; Ex. 1025, at 256). Additionally, Petitioner relies on Brooks and Arthur as evidence explaining that the subcutaneous route is more advantageous than the intramuscular route. *Id.* at 45–47 (quoting Ex. 1008, at 91) (citing Ex. 1023, at 257).

Patent Owner is correct that Petitioner has not provided any arguments in support of combining Insulin Admin. with Wyeth, but Petitioner does not rely on Insulin Admin. as disclosing any of the limitations of claims 1–6, 11–13, 17, 18, and 22. *See id.* at 38–44. Accordingly, we do not include Insulin Admin. in this ground in instituting *inter partes* review.

b. Claims 7–10, 14–16, and 19–21

As for claims 7–10, 14–16, and 19–21, Petitioner’s claim charts cross reference the claim charts to the obviousness grounds in which Grint (not Wyeth) is applied as the primary reference. *See* Pet. 41–44. Although the previous claim charts identify portions of Arthur, Moitra, and Insulin Admin. that correspond with the claim limitations at issue (*see id.* at 23–25), Petitioner gives no reason why it would be obvious to combine the Arthur, Moitra, and Insulin Admin. references with Wyeth in the context of these claims. Instead, the entirety of Petitioner’s argument is that these claims “would have been obvious for the reasons set forth in the claim chart and discussion in Section VI.B, *supra.*” *Id.* at 48.¹² The claim chart and discussion in Section VI.B of the Petition, however, relate to the combination of Arthur, Moitra, and Insulin Admin. with Grint. Thus, the Petition fails to provide sufficient detail as to why it would have been obvious to one of ordinary skill in the art to combine the disclosures of Arthur, Moitra, and Insulin Admin., with Wyeth, in order to meet the limitations of claims 7–10, 14–16, and 19–21. *See* 37 C.F.R. § 42.22(a)(2)

¹² The Petition also includes claims 11–13 in this argument, but the Petition relies on the primary reference Wyeth as disclosing each limitation of claims 11–13. *See* Pet. 42–43; *id.* at 32–33.

(petition must include “[a] full statement of the reasons for the relief requested, including a detailed explanation of the significance of the evidence”).

I. Secondary Considerations

Factual inquiries for an obviousness determination include secondary considerations based on objective evidence of nonobviousness. *See Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966). Secondary considerations may include long-felt but unsolved need, failure of others, unexpected results, commercial success, copying, licensing, and praise. *Id.* at 17; *Transocean Offshore Deepwater Drilling, Inc. v. Maersk Drilling USA, Inc.*, 699 F.3d 1340, 1349, 1355 (Fed. Cir. 2012).

Patent Owner argues that Petitioner fails to fully address secondary considerations, including evidence of copying and commercial success. Prelim. Resp. 35–36. Patent Owner provides Petitioner’s own press release as evidence of both copying and commercial success. *See id.* at 36 (citing Ex. 2009). Patent Owner also states that Petitioner was aware of the -649 IPR petitioner’s intent to copy the claimed method. *Id.*

Petitioner argues that secondary considerations do not rebut obviousness, but does not address the secondary considerations of copying and commercial success raised by Patent Owner. Pet. 54–60.

At this stage of the proceeding, we are not persuaded that Petitioner’s press release (Ex. 2009) and alleged knowledge of copying by the -649 IPR petitioner are sufficient to outweigh reasons to institute a trial based on certain obviousness challenges. The issue of secondary considerations is highly fact-specific. At this stage of the proceeding, the record regarding such secondary considerations is incomplete.

J. Remaining Grounds

The remaining three grounds challenge the same claims as those previously discussed. *See* Pet. 10, 48–54. We exercise our discretion in declining to proceed on these additional obviousness grounds of unpatentability. *See* 37 C.F.R. § 42.108(a).

III. CONCLUSION

For the foregoing reasons, we determine that the information presented in the Petition establishes that there is a reasonable likelihood that Petitioner would prevail in showing that claims 1–22 of the '231 patent are unpatentable.

Specifically, we determine that there is a reasonable likelihood that Petitioner would prevail in showing that (i) claims 1, 2, 4–6, 11–13, 17, and 22 are anticipated by Grint (Ex. 1003); (ii) claims 7–10, 14–16, and 19–21 are obvious over Grint, Arthur (Ex. 1023), Moitra (Ex. 1025), and Insulin Admin. (1015); (iii) claim 18 is obvious over Grint and Alsufyani (Ex. 1006); (iv) claims 1–6, 11–13, 17, 18, and 22 are anticipated by Wyeth (Ex. 1021); and (v) claims 1–6, 11–13, 17, 18, and 22 are obvious over Wyeth, Brooks (Ex. 1008), Arthur, and Moitra. As discussed, we do not include Insulin Admin. in ground (v). We deny institution as to Petitioner's challenge to claims 7–10, 14–16, and 19–21 as being obvious over Wyeth, Brooks, Arthur, Moitra, and Insulin Admin. We also exercise our discretion and decline to institute *inter partes* review on the remaining grounds of unpatentability challenged in the Petition.

At this stage of the proceeding, the Board has not made a final determination as to the patentability of any challenged claim.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that pursuant to 35 U.S.C. § 314(a), an *inter partes* review is instituted as to claims 1–22 of the '231 patent on the following grounds of unpatentability:

A. Claims 1, 2, 4–6, 11–13, 17, and 22 under 35 U.S.C. § 102(b) as anticipated by Grint;

B. Claims 7–10, 14–16, and 19–21 under 35 U.S.C. § 103(a) as unpatentable over Grint, Arthur, Moitra, and Insulin Admin.;

C. Claim 18 under 35 U.S.C. § 103(a) as unpatentable over Grint and Alsufyani;

D. Claims 1–6, 11–13, 17, 18, and 22 under 35 U.S.C. § 102(b) as unpatentable over Wyeth; and

E. Claims 1–6, 11–13, 17, 18, and 22 under 35 U.S.C. § 103(a) as unpatentable over Wyeth, Brooks, Arthur, and Moitra;

FURTHER ORDERED that no other proposed grounds of unpatentability are authorized; and

FURTHER ORDERED that pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial commencing on the entry date of this decision.

IPR2016-01370
Patent 8,664,231 B2

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