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Paper 90
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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS INC. and AMNEAL PHARMACEUTICALS LLC,
Petitioners,

v.

YEDA RESEARCH & DEVELOPMENT CO. LTD.,
Patent Owner.

Case IPR2015-00643
Patent 8,232,250 B2[1]

Before SHERIDAN K. SNEDDEN, ZHENYU YANG, and TINA E. HULSE, *Administrative Patent Judges*.

YANG, *Administrative Patent Judge*.

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

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[1] Case IPR2015-01976 has been joined with Case IPR2015-00643.

I. INTRODUCTION

Mylan Pharmaceuticals Inc. ("Petitioner") filed a Corrected Petition (Paper 7 ("Pet.")), seeking an *inter partes* review of claims 1–20 of U.S. Patent No. 8,232,250 B2 ("the '250 patent," Ex. 1001). Yeda Research and Development Co., Ltd. ("Patent Owner") filed a Preliminary Response. Paper 10 ("Prelim. Resp."). On August 25, 2015, the Board instituted a review of the patentability of the challenged claims. Paper 13 ("Dec.").

Thereafter, Patent Owner filed a Response (Paper 26 ("PO Resp.")), and Petitioner filed a Reply (Paper 58 ("Reply")). The parties also briefed whether certain exhibits should be excluded from the record. Papers 67, 69, 72, 75, 79, 80. In addition, Patent Owner filed observations on the cross-examination of Petitioner's reply declarants (Paper 71), and Petitioner filed a response thereto (Paper 77). An oral hearing for this proceeding was held on May 11, 2016. *See* Paper 84 ("Tr.")

On September 25, 2015, Amneal Pharmaceuticals LLC filed a Petition requesting an *inter partes* review of claims 1–20 of the '250 patent in case IPR2015-01976. Amneal also filed a motion to join its case with this proceeding. IPR2015-01976, Paper 3. On December 28, 2015, we granted Amneal's Petition and motion for joinder, terminated IPR2015-01976, and joined it with this case. *Id.*, Paper 9.

The Board has jurisdiction under 35 U.S.C. § 6. On August 24, 2016, we entered a Final Written Decision pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73. Patent Owner filed a request for rehearing of our decision. Paper 87. In a concurrently issued Order, we grant-in-part Patent Owner's request and vacate our original decision. Paper 89. We hereby issue this modified Final Written Decision.

For the reasons provided below, we determine that Petitioner has met its burden of proving the unpatentability of claims 1–20 of the '250 patent by a preponderance of the evidence. *See* 35 U.S.C. § 316(e).

A. Related Proceedings

The parties have been litigating over the '250 patent in the following two district court cases: *Teva Pharmaceuticals USA, Inc. v. Mylan Pharmaceuticals Inc.*, 14-cv-01278 (D. Del., Oct. 6, 2014), and *Teva Pharmaceuticals USA, Inc. v. Mylan Pharmaceuticals Inc.*, 14-cv-00167 (N.D. W. Va., Oct. 7, 2014). Pet. 1, 2; Paper 6, 2. The '250 patent is also the subject of several other district court cases that do not involve Petitioner. Pet. 1, 2; Paper 6, 2.

Petitioner also filed two other petitions, challenging two patents by Patent Owner: IPR2015-00644 (US 8,399,413 B2) and IPR2015-00830 (US 8,969,302 B2). We instituted *inter partes* reviews in those cases too.

B. The '250 Patent

The '250 patent is directed to a method of alleviating a symptom of relapsing-remitting multiple sclerosis ("RRMS") using glatiramer acetate ("GA"). Ex. 1001, Abstract, 2:55–64. RRMS is a form of multiple sclerosis ("MS"), an autoimmune disease that affects the central nervous system. *Id.* at 1:18–20, 1:31. "Patients suffering from RRMS experience sporadic exacerbations or relapses, as well as periods of remission." *Id.* at 1:32–33.

GA is a mixture of polypeptides that do not all have the same amino acid sequence. *Id.* at 1:65–2:16. Before the '250 invention, the FDA approved 20 mg GA daily injection (under the tradename Copaxone®) for treating patients with RRMS. *Id.* at 2:17–20. The '250 patent discloses an

effective low frequency dosage regimen of GA administration to patients suffering from RRMS. *Id.* at 2:47–51.

C. Illustrative Claim

Claims 1, 15, and 19 are independent claims. Claim 1 is illustrative. It reads:

> 1. A method of alleviating a symptom of relapsing-remitting multiple sclerosis in a human patient suffering from relapsing-remitting multiple sclerosis or a patient who has experienced a first clinical episode and is determined to be at high risk of developing clinically definite multiple sclerosis comprising administering to the human patient a therapeutically effective regimen of three subcutaneous injections of a 40 mg dose of glatiramer acetate over a period of seven days with at least one day between every subcutaneous injection, the regimen being sufficient to alleviate the symptom of the patient.

Claim 15 is similar to claim 1, except it is directed to a method of increasing the tolerability of GA treatment in an RRMS patient, and requires the regimen to do so. Claim 19 is also similar to claim 1, except it is directed to a method of reducing frequency of relapses in an RRMS patient, and requires the regimen to do so.

D. Reviewed Grounds of Unpatentability

We instituted trial based on the following grounds of unpatentability:

Claims	Basis	References
1–20	§ 103	Pinchasi[2] and the 1996 SBOA[3]
1–20	§ 103	Pinchasi and Flechter[4]

II. ANALYSIS

In support of their respective positions, Petitioner relies on the Declarations of Drs. Stephen J. Peroutka (Ex. 1003), Ari Green (Exs. 1004, 1085), and Joel W. Hay (Ex. 1099), and Patent Owner relies on the Declarations of Drs. Edward J. Fox (Ex. 2129), Henry G. Grabowski (Ex. 2133), Robert William Gristwood (Ex. 2134), and Tjalf Ziemssen (Ex. 2135).

A. Principles of Law

To prevail in this *inter partes* review of the challenged claims, Petitioner must prove unpatentability by a preponderance of the evidence. 35 U.S.C. § 316(e); 37 C.F.R. § 42.1(d).

A patent claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the claimed subject matter and the prior art are such that the subject matter, as a whole, would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said

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[2] Irit Pinchasi, WO 2007/081975 A2, published July 19, 2007 (Ex. 1005).
[3] Summary Basis of Approval ("SBOA") for the New Drug Application for 20 mg daily Copaxone ® (NDA #20-622) (Ex. 1007).
[4] S. Flechter et al., *Copolymer 1 (Glatiramer Acetate) in Relapsing Forms of Multiple Sclerosis: Open Multicenter Study of Alternate-Day Administration*, 25 CLINICAL NEUROPHARM. 11–15 (2002) (Ex. 1008).

subject matter pertains. *KSR Int'l Co. v. Teleflex Inc*., 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations, including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of skill in the art; and (4) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966). The strength of each of the *Graham* factors must be weighed in every case and must be weighted en route to the final obviousness determination. *See, e.g.*, *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538–39 (Fed. Cir. 1983) (instructing that evidence of secondary considerations, when present, must always be considered in determining obviousness).

"[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR*, 550 U.S. at 418. "[I]t can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine elements in the way the claimed new invention does." *Id*. Moreover, a person of ordinary skill in the art must have had a reasonable expectation of success of doing so. *PAR Pharm., Inc. v. TWi Pharms., Inc.*, 773 F.3d 1186, 1193 (Fed. Cir. 2014).

We analyze the instituted grounds of unpatentability in accordance with these principles.

B. Claim Construction

In an *inter partes* review, the Board interprets a claim term in an unexpired patent according to its broadest reasonable construction in light of the specification of the patent in which it appears. 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144–46 (2016). Under

that standard, and absent any special definitions, we assign claim terms their ordinary and customary meaning, as would be understood by one of ordinary skill in the art at the time of the invention, in the context of the entire patent disclosure. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007).

In the Decision to Institute, we determined that under the broadest reasonable interpretation, the claims do not encompass an alternate-day administration schedule (i.e., one that administers the drug three times in one week and four times the next). Dec. 5–7. We also concluded that there is a typographic error in claim 3, and treated claim 3 as depending directly from claim 2 and indirectly from claim 1. *Id.* at 7–8. During trial, the parties did not dispute this determination. Having considered the complete record developed at trial, we see no reason to change our interpretation of the claims.

C. Prior Art Disclosures

Pinchasi relates to a method of alleviating a symptom of an RRMS patient. Ex. 1005, 9.[5] The method comprises periodically administering by subcutaneous injection a 40 mg dose of GA. *Id.* Pinchasi discloses that the GA can be administered daily or every other day. *Id.* It also discloses that the alleviated symptom can be the frequency of relapses. *Id.*

The 1996 SBOA is a compilation of documents relating to the approval for the New Drug Application ("NDA") for 20 mg Copaxone®.

[5] Unless stated otherwise, we cite to the page numbers provided by the parties in the lower right hand corner of the exhibits, pursuant to 37 C.F.R. § 42.63(d)(2).

Ex. 1007. It includes a review and evaluation of clinical data submitted by the sponsor of the NDA, Teva Pharmaceuticals, USA ("Teva"). *Id.* at 24–124. It also includes a review of the pharmacology and toxicology studies submitted by Teva. *Id.* at 125–292. The NDA was approved on December 20, 1996. *Id.* at 4.

Flechter reports the results of a multicenter study treating patients with relapsing MS with 20 mg doses of Copolymer 1 (i.e., GA) on alternate days. Ex. 1008, 1. Flechter states that the results of the trial "suggest that alternate-day treatment with Copolymer 1 is safe, well tolerated, and probably as effective as daily Copolymer 1 in reducing relapse rate and slowing neurologic deterioration." *Id.* at 5. Flechter concedes, however, that its study "was uncontrolled," that its conclusions "cannot be used to prove efficacy," and that "these preliminary observations will have to be examined in larger studies." *Id.*

D. The Level of Ordinary Skill in the Art

The parties dispute the proper definition of a person of ordinary skill in the art. Petitioner contends that a person of ordinary skill in the art would have had (1) several years of experience in the pharmaceutical industry or in practicing medicine; (2) experience with the administration or formulation of therapeutic agents, dosing schedules and frequencies, and drug developmental study and design; and (3) a Ph.D. in pharmacology or an M.D. with experience in clinical pharmacology. Pet. 13. In its Preliminary Response, Patent Owner asserted that a skilled artisan would have had knowledge of, and experience with, both MS and GA. Prelim. Resp. 33–34.

In the Decision to Institute, we agreed with Patent Owner. Dec. 9. We noted that Dr. Green, one of Petitioner's declarants, states that a person

of ordinary skill in the art would have had "direct experience administering therapeutic agents for the treatment of MS, as well as familiarity with the dosing schedules and frequencies of the different therapeutic agents available for MS treatment." *Id.* (citing Ex. 1004 ¶ 27).

During trial, neither party contests our findings of the level of a person of ordinary skill in the art. Upon considering the full record, we see no reason to deviate from our prior determination. Thus, we reiterate that in addition to the qualifications specified by Petitioner, a person of ordinary skill in the art would also have experience treating MS with GA.

E. Obviousness over Pinchasi and the 1996 SBOA

Petitioner argues that claims 1–20 are unpatentable as obvious over Pinchasi and the 1996 SBOA. Pet. 51–55. After reviewing the entire record, we determine that Petitioner has established by a preponderance of the evidence that claims 1–20 are unpatentable over Pinchasi and the 1996 SBOA.

As an initial matter, we note that, in its Preliminary Response, Patent Owner challenged the status of the 1996 SBOA as a printed publication under 35 U.S.C. § 102(b). Prelim. Resp. 47–48. In the Decision to Institute, we determined that, based on the record available then, the 1996 SBOA constitutes prior art under § 102(b). Dec. 12–13. In its Response, Patent Owner does not dispute this finding. Having considered the complete record developed at trial, we reiterate that Petitioner has presented sufficient evidence (*see* Ex. 1007) to show that the 1996 SBOA was publicly accessible at least by July 17, 2007, more than one year before the earliest

possible priority date of the '250 patent (i.e., August 20, 2008). *See* Dec. 12–13. Thus, the 1996 SBOA constitutes prior art under § 102(b).

Claims 1 and 19

Petitioner contends that claims 1 and 19 would have been obvious over Pinchasi and the 1996 SBOA. Pet. 52–54.

Specifically, Petitioner argues that Pinchasi teaches a method for alleviating a symptom in an RRMS patient, wherein the symptom is the "frequency of relapses," as recited in the preambles of claims 1 and 19. *Id.* at 23–24 (citing Ex. 1005, 9:2–4, 9:12–13). Patent Owner does not dispute this assertion. Petitioner also relies on Pinchasi for teaching subcutaneous injection of 40 mg of GA in each dose, the same amount recited in claims 1 and 19. *Id.* at 24 (citing Ex. 1005, 6:2–8). Patent Owner does not dispute this contention, either. Based on the full record developed at trial, and for the reasons stated in the Petition (*see* Pet. 23–26) and the testimony of Dr. Green (*see* Ex. 1004 ¶¶ 87–89), we are persuaded that Pinchasi teaches each limitation of claims 1 and 19, except for the requirement of three doses per seven-day period.

Petitioner argues that the dosing frequency would have been obvious because an ordinary artisan would have considered six doses over two seven-day periods to be therapeutically equivalent to, and have substantially the same pharmacological effect as, seven doses over the same period. Pet. 46 (citing Ex. 1004 ¶¶ 95–107; Ex. 1003 ¶¶ 119–39). Petitioner also contends that an ordinary artisan would have been motivated to modify the dosing regimen of Pinchasi to exactly three injections per seven-day period to reduce the frequency of injections, which would reduce the frequency of side effects, and to allow for a more convenient dosing schedule, which

would improve patient compliance. *Id.* at 46–47 (citing Ex. 1004 ¶¶ 93–94; Ex. 1003 ¶¶ 100–03).

In addition, Petitioner notes that a reviewer of the 1996 SBOA "recommend[ed] that [Teva] evaluate the necessity of daily [subcutaneous] injections as opposed to more infrequent intermittent administration of the drug." *Id.* at 43 (citing Ex. 1007, 252). Furthermore, Petitioner asserts that the 1996 SBOA teaches that the half-life for Copaxone is approximately 80 hours in a Cynomolgus monkey. *Id.* at 52 (citing Ex. 1007, 197) According to Petitioner, pharmacokinetic data from such a monkey was a reliable model for predicting human pharmacokinetic parameters and creating dosing schedules. *Id.* (citing Ex. 1003 ¶ 120). Thus, Petitioner argues that a person of ordinary skill in the art would have understood that the "injection frequencies could be reduced as far as approximately once every 80 hours while maintaining the same safety and tolerability profiles." *Id.* at 53 (citing Ex. 1003 ¶¶ 132–33).

Patent Owner counters that an ordinary artisan would not have used 40 mg of GA on any dosing schedule, and would not have used a three times per week regimen. PO Resp. 17–32. Patent Owner also argues that there was no motivation to combine Pinchasi with the 1996 SBOA. *Id.* at 32–35. Finally, Patent Owner argues that an ordinary artisan would not have had a reasonable expectation of success that a 40 mg dose of GA three times a week would be therapeutically effective. *Id.* at 36–50.

Upon reviewing the entire trial record, and for the reasons explained in the Petition and by Petitioner's expert, Dr. Green, we find that a person of ordinary skill in the art would have had a reason to modify the dosing

regimen of 40 mg of GA every other day taught in Pinchasi to 40 mg of GA three times over a period of seven days.

In particular, we credit the testimony of Dr. Green, who notes that Pinchasi demonstrates increased efficacy with 40 mg GA when compared to 20 mg GA with no significant difference in side effects. Ex. 1004 ¶¶ 61, 95, 99. Indeed, Pinchasi concludes:

> The increased efficacy observed with 40 mg/day GA in reducing MRI-measured disease activity and relapse rate indicates that it is well tolerated and can improve the treatment of RRMS patients. The improvement in efficacy, however, is not accompanied by a corresponding increase of adverse reactions which would be expected upon a doubling of the administered dose.
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> Also observed was the accelerated rate at which the 40 mg/day dose became effective as compared to the 20 mg/day dose. This was unexpected. Specifically, the 40 mg/day dose showed efficacy, as measured by MRI, by the third month, whereas the 20 mg/day dose did not show efficacy until the sixth month.

Ex. 1005, 20:8–21:6; *see also* Ex. 1006 (concluding daily administration of 40 mg GA was effective, safe and well tolerated). We are therefore persuaded by Dr. Green's testimony that Pinchasi would have strongly suggested to an ordinary artisan to use 40 mg GA for RRMS patients. *See* Ex. 1004 ¶ 100.

Patent Owner argues that a person of ordinary skill in the art would not have used 40 mg of GA because a later phase III clinical trial (the "FORTE trial") demonstrated that 40 mg of GA was not more effective than 20 mg of GA, and 40 mg of GA was associated with more frequent adverse events. PO Resp. 17–20. Upon considering the evidence as a whole, we are not persuaded. The FORTE trial found that "the 40 mg dose did not

demonstrate *increased* efficacy in reducing the relapse rate." Ex. 2001, 1 (emphasis added). At the same time, however, it noted that "the higher [40 mg] dose maintained the favorable safety and tolerability profile of COPAXONE® 20mg." *Id.* Because nothing in FORTE criticizes, discredits, or discourages the use of 40 mg of GA, we determine that FORTE does not teach away from the use of 40 mg of GA. *See In re Fulton*, 391 F.3d 1195, 1201 (Fed. Cir. 2004) (finding "[t]he prior art's mere disclosure of more than one alternative does not constitute a teaching away from any of these alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed").

Upon considering the evidence as a whole, we also find that an ordinary artisan would have been motivated to administer GA three times over a period of seven days to increase patient compliance. We note again that Pinchasi teaches administering 40 mg GA every other day, which equates to seven doses over two weeks. Ex. 1005, 9. Thus, the difference between the challenged claims (three doses over a period of seven days, or six doses over two weeks) and the prior art is one less injection every two weeks.

Dr. Green testifies that it was a well-known principle that decreasing the frequency of injections would have a positive impact on patients to stay on course with treatment. Ex. 1004 ¶ 101. The desirability of less frequent injections is supported by the 1996 SBOA, in which the reviewer recommended that Teva evaluate the necessity of daily injections as opposed to more infrequent intermittent administration of Copaxone®. Ex. 1007, 252.

Other prior art references also support Dr. Green's testimony that less frequent injections of GA is preferred. For example, both Khan 2008[6] (Ex. 1010) and Caon 2009[7] (Ex. 1011) report a pilot trial comparing the effect of 20 mg of GA daily ("QD") versus every other day ("QOD").[8] "After 2 years, there was no difference in the relapse rate, disease progression," or any other tested parameters. Ex. 1011; *see also* Ex. 1010 (stating the same). Afterwards, "patients in each group were given the option to continue or to switch to the other group," and "all patients in the QD group opted to switch to QOD." Ex. 1011; *see also* Ex. 1010 (stating the same). According to both references, "[a]fter a total of 4 years of prospective follow-up, there was no difference between the QD-QOD cross over group and the always QOD group." Exs. 1010, 1011. As a result, both Khan 2008 and Caon 2009 suggest that the 20 mg of GA daily and every-other-day dosing may be equally effective in treating RRMS. Exs. 1010, 1011.

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[6] Khan et al., *Randomized, Prospective, Rater-Blinded, Four-Year, Pilot Study to Compare the Effect of Daily Versus Every-Other-Day Glatiramer Acetate 20 mg Subcutaneous Injections in Relapsing-Remitting Multiple Sclerosis*, 14 MULTIPLE SCLEROSIS S296 (2008) (Ex. 1010) ("Khan 2008").
[7] Caon et al., *Randomized, Prospective, Rater-Blinded, Four-Year, Pilot Study to Compare the Effect of Daily Versus Every-Other-Day Glatiramer Acetate 20 mg Subcutaneous Injections in RRMS*, 72 NEUROLOGY A317 (Mar. 17, 2009) (Ex. 1011) ("Caon 2009").
[8] The parties' declarants agree that Khan 2008 and Caon 2009 describe the same pilot study. Ex. 1085 ¶ 18; Ex. 2135, 72 n.2.

Khan 2009 (Ex. 1089)[9] teaches another pilot study, which compares 20 mg of GA daily versus *twice-a-week* dosing. Although Khan 2009 was published three weeks after the priority date of the '250 patent, Khan 2009 reports the results of a two-year study.[10] Ex. 1089, 2. In other words, the study in Khan 2009 commenced nearly two years before the priority date of the '250 patent. We, therefore, find that Khan 2009 is probative of the fact that those skilled in the art were motivated to investigate dosing regimens of GA with fewer injections to improve patient compliance.

Indeed, Khan 2009 teaches that despite that the researchers had "previously shown that GA administered on alternate days appears to be as effective as daily GA. There [wa]s considerable interest in studying a more patient friendly dosing regimen of GA that may be as efficacious and better tolerated than daily GA." *Id.* at 1. Khan 2009 reported that the relapse rate, disease progression, and many other tested parameters were similar in the two groups. *Id.* at 2. Moreover, "the incidence of lipoatrophy, local injection site reactions, and immediate post injection systemic reactions were significantly lower in the GA twice-weekly group." *Id.* Khan 2009 concludes: "This study provides further evidence that GA administered less frequently than daily may be as efficacious and better tolerated than GA administered daily. This may have a significant impact on improving

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[9] Khan et al., *Glatiramer Acetate 20 mg Subcutaneous Twice-Weekly Versus Daily Injections: Results of a Pilot, Prospective, Randomized, and Rater-Blinded Clinical and MRI 2-Year Study in Relapsing Remitting Multiple Sclerosis*, 15 MULTIPLE SCLEROSIS S249 (2009) (Ex. 1089, "Khan 2009").
[10] Patent Owner has moved to exclude Khan 2009. We deny Patent Owner's motion for the reasons stated in more detail below.

compliance and tolerability while maintaining the desired immunomodulating effect of GA." *Id.*

Dr. Green also testifies that the "three-times weekly" dosing schedule means the administration would take place on the same day each week, for example on Monday, Wednesday, and Friday. Ex. 1004 ¶ 94. According to Dr. Green, this is easier to follow and maintain than the every-other-day dosing schedule, which would occur on different days of the week throughout the month. *Id.* ¶¶ 94, 106. In light of the evidence as a whole, we are persuaded that an ordinary artisan would have understood the benefits of less frequent injections and, therefore, had a reason to reduce Pinchasi's dosing regimen to three times over a period of seven days.

We further find that a person of ordinary skill in the art would have had a reasonable expectation of success in administering 40 mg of GA three times a week. We credit Dr. Green's testimony that an ordinary artisan would have considered GA to be a "forgiving drug." Ex. 1085 ¶ 19. Dr. Green testifies that it was a standard instruction for patients who miss a dose to skip the dose rather than take a double dose. *Id.* (citing Ex. 1086[11]); Ex. 1004 ¶ 33 (citing Ex. 1058). Indeed, prior art teaches: "If you miss a dose [of GA], take it as soon as you remember. If you do not remember until the following day, skip the missed dose and continue with your regular dosing schedule." Ex. 1058, 3. Teva, the marketer of COPAXONE®, instructs the patients the same way: "If you miss a dose, take your COPAXONE® as soon as you remember. If it is nearer to the time of your

[11] Patent Owner has moved to exclude Ex. 1086. We deny Patent Owner's motion, for the reasons stated in more detail below.

next scheduled dose, skip the missed dose and resume your usual dosing schedule."). Ex. 1086, 2.

Dr. Green further explains that the wide range of likely efficacious doses suggests the forgiving nature of GA. Ex. 1085 ¶¶ 5, 20–21. Each of Flechter and Khan 2008/Caon 2009 teaches administering 20 mg of GA every other day (i.e., 70 mg per week), whereas Pinchasi teaches GA can be administered at 40 mg daily (i.e., 280 mg per week). Exs. 1005, 1008, 1010, 1011. Petitioner argues that 40 mg three times a week (i.e., 120 mg per week) is in the middle range of known effective weekly doses and is close to the FDA-approved 20 mg daily regimen (140 mg per week). Pet. 43; Reply 9 (citing Ex. 1085 ¶¶ 15–21). We find Dr. Green's explanation and Petitioner's argument persuasive.

Patent Owner contends that a person of ordinary skill in the art would not have found the claimed dosing regimen obvious because the mechanism of action of GA was still unknown, which would have taught away from three times weekly dosing. PO Resp. 22–28. According to Patent Owner and its declarant, Dr. Ziemssen, at the time of the invention, the beneficial effects of GA were generally thought to be brought about by increasing the population of GA-reactive Th2 cells. *Id.* at 24 (citing Ex. 2135 ¶¶ 58–64). Patent Owner asserts that an ordinary artisan "would have believed that a constant supply of Th2 cells reaching the CNS would be required to continuously counter-balance the pro-inflammatory effects of Th1 cells that are repeatedly generated in patients in MS." *Id.* at 25 (citing Ex. 2135 ¶¶ 43–64). As such, Patent Owner contends that one of ordinary skill in the art "would have believed that administering the drug *even more frequently*

than once daily would be the best way to enhance efficacy." *Id.* at 25 (citing Ex. 2135 ¶ 150). We are not persuaded.

Numerous prior art references studying less frequent dosing contradict Dr. Ziemssen's opinion. *See, e.g.*, Ex. 1005 (Pinchasi dosing every other day); Ex. 1008 (Flechter dosing every other day); Ex. 1010 (Khan 2008 dosing every other day), Ex. 1089 (Khan 2009 dosing twice a week). Indeed, all those studies demonstrated that less-than-daily dosing of GA is as effective as daily dosing. Specifically, both Khan 2008 and Caon 2009 report that, during the two years of studying the effect of daily versus every-other-day dosing of GA, "Th1/Th2 cytokine expression did not differ between the two groups at any time point after randomization." Exs. 1010, 1011.

We also credit the testimony of Dr. Green, who explains that, given the uncertainty regarding GA's mechanism of action, a person of ordinary skill in the art would not rely on any single theory in deciding which mechanism to pursue. Ex. 1085 ¶ 44. Dr. Green continues, stating that "[i]f anything, the uncertainty surrounding GA's mechanism of action would motivate a POSA to investigate dosing regimens with existing and even preliminary clinical support." *Id.*

Patent Owner further argues that a person of ordinary skill in the art would not have combined Pinchasi with the 1996 SBOA to arrive at the claimed dosing regimen. PO Resp. 32–35. Patent Owner contends that, although Pinchasi discloses the use of 40 mg of GA, the later FORTE results would have caused an ordinary artisan to discard the 40 mg dose altogether. *Id.* at 32–33. Patent Owner also notes that Pinchasi does not suggest dosing

three times weekly, and that the 1996 SBOA does not cure either deficiency of Pinchasi. *Id.* at 33–34.

As explained above, we reject Patent Owner's argument that Pinchasi teaches away from the use of 40 mg of GA. As for the three-times-weekly dosing regimen, Patent Owner asserts that an ordinary artisan would have ignored the suggestion for less frequent dosing in the 1996 SBOA because the suggestion was based on the erroneous belief that GA was acting as a "peptide vaccine." *Id.* at 33. We are not persuaded.

Dr. Green testified that it did not matter to an ordinary artisan in 2009 that GA was not a peptide vaccine because all prior art observations in the clinic made it clear that daily injections were unnecessary. Ex. 1065, 151:24–155:5. We agree that, even if an ordinary artisan knew GA was not a peptide vaccine in 2009, the 1996 SBOA must still be read in the context of the prior art as a whole, which suggested less frequent dosing of GA was desirable. *See In re Merck & Co.*, 800 F.2d 1091, 1097 (Fed. Cir. 1986) (stating prior art "must be read, not in isolation, but for what it fairly teaches in combination with the prior art as a whole"); *see also In re Young*, 927 F.2d 588, 591 (Fed. Cir. 1991) ("[A] reference which disclosed obsolete technology remained in the prior art. This court considered the reference for what it disclosed in relation to the claimed invention.").

Finally, Patent Owner asserts that a person of ordinary skill in the art would not have had a reasonable expectation of success that the claimed dosing regimen would be effective. PO Resp. 36–50. We understand pharmaceutical development is an unpredictable art. At the same time, we keep in mind that an obviousness inquiry does not require absolute predictability. *In re Longi*, 759 F.2d 887, 896 (Fed. Cir. 1985). Indeed, as

the Federal Circuit has explained, simply because the formation and properties of a new drug must be verified through testing does not mean that the formulation would have not been obvious, "since the expectation of success need only be reasonable, not absolute." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007).

Patent Owner argues that because there was no data establishing the successful use of 40 mg of GA on alternate days, "the question is not whether there would have been an expectation of success when moving from alternate day administration of 40 mg of GA . . ., but the expectation when moving from 20 mg daily to 40 mg three times weekly." *Id.* at 37. Even if an ordinary artisan came upon the idea of using 40 mg GA three times weekly, Patent Owner argues, there is nothing in the prior art to support a reasonable expectation of success. *Id.*

Having considered Petitioner and Patent Owner's arguments, we find Petitioner has the better position. As Dr. Green explains, a person of ordinary skill in the art reading Pinchasi would conclude that 40 mg daily is not inferior to 20 mg daily. Ex. 1085 ¶ 76. And based on Flechter and Khan 2008/Caon 2009, an ordinary artisan would reasonably expect 20 mg every other day to be efficacious. *Id.* ¶ 77. Thus, we are persuaded by Dr. Green's testimony that a person of ordinary skill in the art would reasonably expect 40 mg administered every other day to be efficacious. *Id.*

Dr. Green explains that Flechter and Pinchasi teach a therapeutically effective range of dosing for GA of 70 mg per week (20 mg every other day disclosed in Flechter) to 280 mg per week (40 mg daily disclosed in Pinchasi). Ex. 1085 ¶ 16. According to Dr. Green, "40 mg was a logical dosage choice for investigating three-times-weekly administration because it

kept the total weekly dose (120 mg) similar to the FDA-approved weekly dose (140 mg)." *Id.* ¶ 77.

Patent Owner contends that Petitioner's argument is "simplistic" because "the prior art does not establish that GA's efficacy could be maintained by increasing the dose to 40 mg and reducing the frequency of dosing to three times per week." PO Resp. 47. According to Patent Owner, an ordinary artisan would not know whether the altered regimen would work. *Id.* Conclusive proof of efficacy, however, is not required to show obviousness. *See Hoffmann-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1331 (Fed. Cir. 2014) ("Conclusive proof of efficacy is not necessary to show obviousness. All that is required is a reasonable expectation of success.").

Thus, we are persuaded by Dr. Green's conclusion that an ordinary artisan would have had a reasonable expectation of success because the claimed regimen at 120 mg per week is within the dosing range known to be therapeutically effective, and nearly identical to the FDA-approved 20 mg daily dosing regimen of 140 mg per week. *See* Ex. 1085 ¶ 16. Moreover, as discussed above, nearly two years before the priority date of the '250 patent, Khan 2009 commenced its study on 20 mg GA administered *twice-a-week*, further evincing that an ordinary artisan would have had a reasonable expectation of success in pursuing a 40 mg, three-times-weekly GA dosing regimen. *See* Ex. 1089.

In sum, upon considering the evidence as a whole,[12] we determine that the combination of Pinchasi and the 1996 SBOA teaches or suggests each limitation of claims 1 and 19, that a person of ordinary skill in the art would have had a reason to combine the references and would have had a reasonable expectation of success in dosing 40 mg GA three times over a seven-day period.

Claims 2–14 and 20

Petitioner also contends that claims 2–14 and 20 would have been obvious over Pinchasi and the 1996 SBOA. Pet. 26–34, 48–49, 55. Patent Owner does not dispute that the combination of Pinchasi and the 1996 SBOA teaches the additional limitations of claims 2–4, 6–8, 12–14, and 20. Based on the full record developed at trial, and for the reasons stated in the Petition and the testimony of Dr. Green, we are persuaded that Pinchasi teaches each limitation of claims 2–4, 6–8, 12–14, and 20. *See id.*

Patent Owner challenges that Petitioner has failed to show that the combination of the prior art teaches the additional limitations of claims 5 and 9–11. PO Resp. 51–53. We disagree with Patent Owner.

Each of claims 5 and 9–11 depends from claim 1, and further recites that wherein alleviating a symptom comprises "reducing brain atrophy," "reducing the number of new hypointense lesions on enhanced T_1 scans in the patient or reducing the total volume of hypointense lesions on enhanced T_1

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[12] We note that Petitioner also relies on pharmacokinetic data (including the half-life for GA) from the Cynomolgus monkey. *See* Pet. 52–53. Patent Owner argues that such data are irrelevant and cannot be extrapolated to humans. PO Resp. 39–45. Because we do not rely on that data for purposes of this Decision, we take no position on the relevance of the data to this proceeding.

scans," "reducing a level of disability as measured by EDSS Score, by the work productivity and activities impairment-General Health (WPAI-GH) questionnaire, or by EuroQoL (EQ5D) questionnaire," and "reducing a change in EDSS Score in the patient or reducing a change in Ambulation Index," respectively.

Patent Owner contends that Petitioner has not set forth any specific argument regarding these limitations. *Id.* at 51. According to Patent Owner, "[n]one of these limitations in the dependent claims are inherently disclosed in Pinchasi." *Id.* As an example, Patent Owner points to the deposition testimony of Dr. Peroutka, one of Petitioner's experts, in which he acknowledged that Pinchasi does not specifically teach reducing brain atrophy. *Id.* at 52 (citing Ex. 1066, 212:6–15). We are not persuaded.

We agree with Petitioner that the additional limitations recited in claims 5 and 9–11 are "well-known beneficial effects" resulting from, and are the natural results of, the administration of a first-line therapy, such as GA. *See* Pet. 28–33 (citing Ex. 1004 ¶¶ 71, 76, 111–12). Indeed, Dr. Green refers to Pinchasi for teaching "reducing the number of new hypointense lesions on enhanced T1 scans," as recited in claim 9. Ex. 1004 ¶ 112 (citing Ex. 1005, 13:22–26, 16:3–8). Citing other prior art references, Dr. Green further opines that one of ordinary skill in the art would have recognized that GA treatment would satisfy the additional limitations recited in claims 5, 10, and 11. *Id.* (citing Exs. 1018, 1025, 1061). We find the testimony of Dr.

Green credible and persuasive. Thus, we determine that prior art teachings as a whole teaches each additional limitation recited in claims 5 and 9–11.

Claims 15–18

Petitioner further contends that independent claim 15 and its dependent claims 16–18 would have been obvious over Pinchasi and the 1996 SBOA. Pet. 49–55.

Claim 15 recites a method of "increasing the tolerability of GA treatment in a human patient" that "comprises reducing frequency" of GA injections from 20 mg daily to 40 mg three times over a period of seven days. In addition to the same argument advanced in relation to claims 1 and 19, Patent Owner contends that the prior art does not teach administering 20 mg GA daily before switching to the 40 mg three-times-weekly dosing regimen, as required in claim 15. PO Resp. 53. Nor does the prior art suggest, according to Patent Owner, that 40 mg three-times-weekly dosing regimen would improve the tolerability of GA. *Id.* We, again, disagree with Patent Owner.

Petitioner contends that, at the time of the invention, an ordinary artisan "would know and understand th[at] ***decreasing*** the number of subcutaneous injections that a patient must endure would increase the tolerability of GA treatment." Pet. 50 (citing Ex. 1003 ¶¶ 101–105; Ex. 1004 ¶¶ 117–118). As Dr. Green pointed out, in Khan 2008 and Caon 2009, all patients treated with 20 mg daily GA injection for two years voluntarily switched to every-other-day dosing. Ex. 1004 ¶ 118 (citing Exs. 1010, 1011). In addition, Caon 2009 reports that injection related lipoatrophy was significantly less in the every-other-day dosing group.

Ex. 1011. In other words, every-other-day dosing decreases the injection related side effects.

In an obviousness inquiry, we must consider the background knowledge possessed by a person having ordinary skill in the art. *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007). As a result, even though Pinchasi and the 1996 SBOA do not specifically disclose the disputed limitations in claim 15, we agree with Petitioner that an ordinary artisan, considering prior art teachings as a whole, would have had a reason to switch patients treated with GA from dosing 20 mg daily to 40 mg three times over a period of seven days, and would have known that doing so would increase the tolerability of GA treatment. For the reasons stated in the Petition, we also find that the combination of Pinchasi and the 1996 SBOA teaches the additional limitations recited in claims 16–18. *See* Pet. 50–51.

Secondary Considerations

"For objective evidence of secondary considerations to be accorded substantial weight, its proponents must establish a nexus between the evidence and the merits of the claimed invention." *In re Huai-Hung Kao,* 639 F.3d 1057, 1068 (Fed. Cir. 2011) (*quoting Wyers v. Master Lock Co.*, 616 F.3d 1231, 1246 (Fed. Cir. 2010)). Where objective indicia "result[ ] from something other than what is both claimed and *novel* in the claim, there is no nexus to the merits of the claimed invention." *Id*. "To the extent that the patentee demonstrates the required nexus, his objective evidence of nonobviousness will be accorded more or less weight." *In re GPAC Inc*., 57 F.3d 1573, 1580 (Fed. Cir. 1995).

Patent Owner argues that the nonobviousness of the challenged claims are supported by secondary considerations, including unexpected results, commercial success, and the satisfaction of a long-felt need. PO Resp. 53–60. We address each argument in turn.

Unexpected Results

Patent Owner's evidence of unexpected results relates to the effectiveness and tolerability of the 40 mg, three-times-weekly as compared to the 20 mg daily GA dosing regimen. *Id.* at 53–56. Patent Owner points to Table 5 of Flechter, which purportedly shows that the mean relapse rate of the alternate-day administration of 20 mg of GA (0.56 ± 1.02) was twice as high as that of the daily administration of 20 mg of GA (0.3 (± 0.5). PO Resp. 54 (citing Ex. 1008, 4). According to Patent Owner, this suggested that "decreasing the frequency of administration of GA would decrease the efficacy of the drug." *Id.* In view of this expectation, Patent Owner argues, it was unexpected that a 40 mg three-times-weekly regimen was as effective as the 20 mg daily product. *Id.* (citing Ex. 2022, 1; Ex. 2129 ¶¶ 36, 40, 45). In addition, Patent Owner contends that it was "surprising and unexpected that the 40 mg three injections weekly regimen was shown to be associated with fewer and less severe injection site reactions than 20 mg daily." *Id.* at 56 (citing Ex. 2029, 3; Ex. 2025, 5; Ex. 2129 ¶¶ 20, 36, 38, 45–46, 54–58). The surprising effectiveness and tolerability of 40 mg three-times-weekly regimen, Patent Owner concludes, support the nonobviousness of the challenged claims. We are not persuaded.

First, we agree with Petitioner and Dr. Green that Patent Owner has misinterpreted the data in Table 5 of Flechter, which compares the non-annualized two-year relapse rate of Flechter's alternate-day treatment with

the annualized two-year relapse rate of the daily treatment reported in Meiner,[13] a different clinical study. Pet. 11–12; Ex. 1085 ¶ 79. When viewed correctly, Flechter teaches a slightly lower relapse rate in patients treated with 20 mg every other day than patients treated with 20 mg every day. *See* Ex. 1085 ¶ 79. Our finding is consistent with the authors' conclusion that the "results of the present alternate-day treatment were slightly better than those of the previous study with daily treatment." Ex. 1008, 4. Thus, we are not persuaded that a person of ordinary skill in the art would interpret Flechter as showing that decreasing the dosing frequency would decrease the efficacy of the drug.

Furthermore, Pinchasi, the closest prior art, teaches administrating 40 mg GA every other day. Ex. 1005, 9:1–11. Thus, the difference between the claimed subject matter and Pinchasi, the closest prior art, is the frequency of dosing. As to such claimed subject matter, "when unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art." *Kao Corp. v. Unilever United States, Inc*., 441 F.3d 963, 970 (Fed. Cir. 2006) (*quoting In re Baxter Travenol Labs*., 952 F.2d 388, 392 (Fed. Cir. 1991)). Here, however, there is insufficient evidence of record showing any unexpected benefit between the claimed three-times-weekly as compared to the prior art every-other-day dosing. Accordingly, we are not persuaded that the nonobviousness of the challenged claims is supported by evidence of unexpected results.

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[13] Meiner et al., *Copolymer 1 in Relapsing-Remitting Multiple Sclerosis: a Multi-Centre Trial, in Frontiers in Multiple Sclerosis: Clinical Research and Therapy* (Abramsky et al. eds., 1997) (Ex. 1009).

Commercial Success

Patent Owner asserts that the commercial success of its marketed 40 mg, three-times-weekly GA product ("Copaxone® 40 mg Product") supports the nonobviousness of the challenged claims. PO Resp. 57–58. According to Patent Owner, the Copaxone® 40 mg Product "has been an enormous commercial success . . . , capturing approximately 66% of the Copaxone® market." PO Resp. 57 (citing Ex. 2024, 9). Patent Owner presents evidence of the amount of sales and number of new prescriptions generated by the Copaxone® 40 mg Product. *Id.* (citing Ex. 2133 ¶¶ 13–14, 26, 28, 31–32). For example, Patent Owner contends that "[a]lthough the product has only been on the market for a mere 20 months, it has generated over $3.5 billion in wholesale sales." *Id.* (citing Ex. 2133 ¶¶ 13, 26). We are not persuaded.

"When a patentee can demonstrate commercial success, usually shown by significant sales in a relevant market, and that the successful product is the invention disclosed and claimed in the patent, it is presumed that the commercial success is due to the patented invention." *J.T. Eaton & Co. v. Atlantic Paste & Glue Co*., 106 F.3d 1563, 1571 (Fed. Cir. 1997); *see also Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1130 (Fed. Cir. 2000) (stating the presumption that commercial success is due to the patented invention applies "if the marketed product embodies the claimed features, and is coextensive with them").

Patent Owner argues that the commercial success of the Copaxone® 40 mg Product is tied to the three-times-weekly dosing regimen required by the challenged claims. PO Resp. 58. Dr. Green, Petitioner's expert, acknowledged the less dosing frequency as the "selling point" of the

Copaxone® 40 mg Product. *Id.* (citing Ex. 1065, 94:25–95:3). Thus, we presume there is a nexus between the Copaxone® 40 mg Product and the claimed invention. *See* Ex. 2133, ¶¶ 35–40.

A party asserting obviousness, however, may rebut the presumed nexus. *Brown & Williamson Tobacco*, 229 F.3d at 1130. Petitioner counters that it was the established Copaxone® brand recognition and steep price discounts, and not the claimed subject matter, that drove the commercial success of the Copaxone® 40 mg Product. Reply 20–21. According to Petitioner,

> To entice Copaxone 20 mg users to switch to Copaxone 40 mg prior to entry of a generic 20 mg product, [Patent Owner] offered its 40 mg product at lower prices than 20 mg daily. [Patent Owner] offered patients a more favorable copay and ensured that 40 mg was the lowest cost GA product on the market—cheaper than even generic Glatopa—through rebates and discounts. Ex. 1099 ¶¶ 25, 27, 29, 53–62. As a result, and as Dr. Grabowski's graphs show, Copaxone 40 mg's sales derive from cannibalization of the 20 mg market. *Id*. ¶¶ 30, 63–65.

Id. Petitioner also contends that Patent Owner fails to account for several competing products, which constituted over $1 billion in U.S. sales in 2015. *Id.* (citing Ex. 1099 ¶¶ 24, 34–43).

We find the Petitioner's evidence persuasive and argument well supported. In its efforts to establish commercial success of the Copaxone® 40 mg Product, Patent Owner appears to have underestimated the market. Nor does it mention any effect pricing and marketing have had on the sales. As a result, we find Petitioner has presented sufficient evidence to rebut the presumed nexus between the commercial success of the Copaxone® 40 mg Product and the claimed invention. *See Brown & Williamson Tobacco*, 229

F.3d at 1130 ("The presumed nexus cannot be rebutted with mere argument; evidence must be put forth.").

In addition, "the asserted commercial success of the product must be due to the merits of the claimed invention beyond what was readily available in the prior art." *J.T. Eaton*, 106 F.3d at 1571 (citing *Richdel, Inc. v. Sunspool Corp.*, 714 F.2d 1573, 1580 (Fed. Cir. 1983) (finding that the patentee failed to show that "such commercial success as its marketed system enjoyed was due to anything disclosed in the patent in suit which was not readily available in the prior art")).

Here, Patent Owner asserts commercial success of the 40 mg, three-times-weekly product as compared to the 20 mg, daily product. There is no evidence comparing the Copaxone® 40 mg Product with Pinchasi, the closest prior art, which teaches a 40 mg, every-other-day dosing regimen, because no such product was available on the market. Petitioner argues that the absence of a competing product is due to Patent Owner's blocking patents on GA and its manufacturing process. Reply 1, 21 (citing *Teva Pharms. USA, Inc. v. Sandoz, Inc.*, 789 F.3d 1335, 1338 (Fed. Cir. 2015)). We agree with Petitioner (*see* Tr. 89:22–90:4) that where "market entry by others was precluded [due to blocking patents], the inference of non-obviousness of [the asserted claims], from evidence of commercial success, is weak." *See Merck & Co. v. Teva Pharm. USA, Inc.*, 395 F.3d 1364, 1376 (Fed. Cir. 2005).

As a result, we find the evidence of commercial success presented by Patent Owner is insufficient to support the nonobviousness of the challenged claims.

Long-Felt Need

Patent Owner further contends that there was a long-felt, but unmet need for a treatment option that improved convenience and tolerability, while offering equivalent safety and efficacy as 20 mg daily GA. PO Resp. 59–60. We are not persuaded.

"Longfelt need is closely related to the failure of others. Evidence is particularly probative of obviousness when it demonstrates both that a demand existed for the patented invention, and that others tried but failed to satisfy that demand." *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1082 (Fed. Cir. 2012). Patent Owner is correct that there was a need for a treatment that would enjoy GA's safety and efficacy but have improved convenience and tolerability. PO Resp. 59. The relevant secondary consideration, however, is "long-felt but unsolved need," not long-felt need in isolation. *Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH*, 139 F.3d 877, 884 (Fed. Cir. 1998).

As explained above, Pinchasi teaches administering 40 mg GA every other day. Ex. 1005, 9:1–11. In addition, Flechter and Khan 2008/Caon 2009 suggest that the 20 mg of GA daily and every-other-day dosing are equally effective in treating RRMS. Exs. 1008, 1010, 1011. In other words, while there may have existed a long-felt need, there also existed solutions to the problem. Indeed, "[w]here the differences between the prior art and the claimed invention are as minimal as they are here, however, it cannot be said that any long-felt need was unsolved." *Geo. M. Martin Co. v. All. Mach. Sys. Int'l LLC*, 618 F.3d 1294, 1304 (Fed. Cir. 2010). Thus, we determine Patent Owner has not presented sufficient evidence of long-felt, but unmet, need to support a nonobviousness conclusion.

In sum, after reviewing the entire record, we determine that the combination of Pinchasi and the 1996 SBOA teaches or suggests each limitation of claims 1–20, that a person of ordinary skill in the art would have had a reason to combine the references and would have had a reasonable expectation of 40 mg of success in dosing GA three times over a seven-day period. We further determine that evidence of the objective indicia i not sufficient to overcome the primary findings. As a result, we conclude that Petitioner has established by a preponderance of the evidence that claims 1–20 are unpatentable over Pinchasi and the 1996 SBOA.

F. Obviousness over Pinchasi and Flechter

Petitioner argues that claims 1–20 of the '250 patent would have been obvious over Pinchasi and Flechter. Pet. 56–57. In addition to the same arguments advanced in rebutting the obviousness challenge over Pinchasi and the 1996 SBOA, Patent Owner further contends a person of ordinary skill in the art would not have had a reason to combine Pinchasi and Flechter. PO Resp. 35–36. We are not persuaded.

Patent Owner asserts that, because Flechter only discloses the use of 20 mg GA, an ordinary artisan would not have considered Flechter to be applicable to the 40 mg dose disclosed in Pinchasi, and would not have been motivated to alter the 20 mg daily to the 40 mg three-times-weekly dosing. *Id.* at 35. "Non-obviousness cannot be established by attacking references individually where the rejection is based on the teachings of a combination of references." *In re Merck*, 800 F.2d at 1097. Flechter teaches alternate-day dosing of 20 mg GA "is safe, well tolerated, and probably as effective as daily dosing of 20 mg GA." Ex. 1008, 5. Petitioner asserts that the dosage amount of the 40 mg three-times-weekly dosing falls "squarely within the

safe and effective ranges established by Pinchasi and Flechter." Pet. 56. We find this argument reasonable. Similar to the reasons discussed above, we determine that a person of ordinary skill in the art, reading Pinchasi and Flechter, would have had a reason to modify the dosing regimen of 40 mg of GA every other day taught in Pinchasi to 40 mg of GA three times over a period of seven days. *See* Pet. 56–57; Ex. 1004 ¶¶ 115–19.

Moreover, relying on the testimony of its declarant, Dr. Ziemssen (Ex. 2135 ¶¶ 86–91), Patent Owner asserts that Flechter indicates that less frequent than daily injections were less tolerable than daily treatment. PO Resp. 35–36. We disagree. Dr. Ziemssen compares the data reporting adverse events in patients in Flechter, who were treated with alternate-day administration of GA, with those in a different cohort of patients in Meiner, who were treated with daily administration of GA. Ex. 2135 ¶ 89. From that comparison, Patent Owner contends that Flechter shows alternate-day administration is less tolerable than daily administration. PO Resp. 35–36.

Dr. Ziemssen, however, qualifies this comparison and explains that a person of ordinary skill in the art "generally would not view this type of cross-study comparison between different study populations as a basis for drawing any comparative conclusions." Ex. 2135 ¶ 87. We agree with this statement. As a result, we are unpersuaded by the conclusion drawn from the *ad hoc* comparison of the data in Flechter with those in Meiner. This is especially so in view of Flechter's conclusion that alternate-day administration of glatiramer acetate was "well tolerated, comparing favorably with the effects of daily injections of Copolymer 1 in patients with relapsing MS." Ex. 1008, 1; *see also id.* at 5 ("The results of this trial suggest that alternate-day treatment with Copolymer 1 is safe, well tolerated,

and probably as effective as daily Copolymer 1 in reducing relapse rate and slowing neurologic deterioration.").

Accordingly, we are not persuaded that a person of ordinary skill in the art considering combining a higher dose of GA with the alternate-day dosing schedule in Flecther would, as Patent Owner asserts, conclude that such a regimen would likely exacerbate the frequency of injection site reactions. *See* PO Resp. 36.

Patent Owner makes no other specific arguments with respect to any other claims and the combination of Pinchasi and Flechter. Having considered the record as a whole, we determine that the combination of Pinchasi and Flechter teaches or suggests each limitation of claims 1–20, that a person of ordinary skill in the art would have had a reason to combine the references and would have had a reasonable expectation of 40 mg of success in dosing GA three times over a seven-day period. *See* Pet. 56–57; Ex. 1004 ¶¶ 115–19. As explained above, we also determine that evidence of the objective indicia is not sufficient to overcome the primary findings. As a result, we conclude that Petitioner has established by a preponderance of the evidence that claims 1–20 are unpatentable over Pinchasi and Flechter.

III. MOTIONS TO EXCLUDE EVIDENCE

A. Patent Owner's Motion to Exclude

Patent Owner filed a Motion to Exclude Exhibits 1068/1089, 1086, 1098, and 1140. Paper 67. Because we do not rely on Exhibits 1098 and 1140 in rendering this Decision, we dismiss Patent Owner's Motion to Exclude these two exhibits as moot. For the following reasons, we deny Patent Owner's Motion to Exclude Exhibits 1068/1089 and 1086.

Exhibit 1068/1089 (Khan 2009) reports the results of a two-year pilot study comparing 20 mg of GA dosed daily or twice a week. Ex. 1089, 1–2. Exhibit 1086 is a printout from Teva's "Shared Solutions" website, which provides online resources and assistance for Copaxone® users. Paper 67, 7. According to Patent Owner, Petitioner relies on these exhibits "to establish a purported teaching prior to August 20, 2009," the apparent priority date of the '250 patent. *Id.* at 7–8. Because Exhibits 1068/1089 and 1086 were published after August 20, 2009, Patent Owner argues, they are not prior art, and should be excluded as irrelevant. *Id.* Patent Owner also contends that any possible probative value of these exhibits is outweighed by "a danger of confusing the issues and wasting time." *Id.* We disagree.

A post-filing date publication is not automatically excluded from consideration as irrelevant. *See, e.g., Plant Genetic Sys., N.V. v. DeKalb Genetics Corp.*, 315 F.3d 1335, 1344 (Fed. Cir. 2003) (approving use of later publications as evidence of the state of art existing on the filing date of an application). Here, although Exhibit 1089 was published three weeks after the priority date of the '250 patent, the study reported therein had commenced two years before. *See* Ex. 1089, 1–2. In other words, Exhibit 1089 reflects that, before the '250 patent invention, those skilled in the art were motivated to investigate dosing regimens with less frequent than daily injections.

Citing Exhibit 1086, Dr. Green states in the Reply Declaration that GA was known to be a forgiving drug. *See* Ex. 1085 ¶ 19 (citing Ex. 1086, 2). Exhibit 1086, however, is not the only evidence Dr. Green relies on to support this testimony. Indeed, in the Declaration supporting the Petition, Dr. Green cites Exhibit 1058. *See* Ex. 1004 ¶ 33. Exhibit 1058 is a printout

of an April 2008 posting about Copaxone®, stating "If you miss a dose, take it as soon as you remember. If you do not remember until the following day, skip the missed dose and continue with your regular dosing schedule. Do not take a double dose to make up for a missed one." Ex. 1058, 3. This is the same as the instruction in Exhibit 1086 cited by Dr. Green. In other words, Exhibit 1086 merely confirms prior art teaching and Dr. Green's testimony that GA has long been known to be a forgiving drug.

In addition, similar to a district court in a bench trial, the Board, sitting as a non-jury tribunal with administrative expertise, is well positioned to determine and assign appropriate weight to evidence presented. In this *inter partes* review, the better course is to have a complete record of the evidence to facilitate public access as well as appellate review. Thus, we deny Patent Owner's Motion to Exclude as to Exhibits 1068/1089 and 1086.

B. Petitioner's Motion to Exclude

Petitioner filed a Motion to Exclude Exhibits 2108–2122, and certain paragraphs in the Grabowski Declaration (Ex. 2133) relying on those exhibits. Paper 69. Patent Owner cites those exhibits and paragraphs in relation to assertions regarding secondary considerations. For the following reasons, we deny Petitioner's Motion to Exclude.

According to Petitioner, Exhibits 2108–2114 and 2120–2122 summarize data compiled from a third party vendor, IMS, into tables and graphs to illustrate purported sales and prescription trends for Copaxone and a subset of other MS treatments. *Id.* at 2. Because the underlying evidence used to create a summary exhibit must be made available and produced to the other party (*id.* (citing Fed. R. Evid. § 1006)), and because the underlying IMS data are not of record in this case (*id.*), Petitioner contends

that Exhibits 2108–2114 and 2120–2122 must be excluded (*id.* at 2–4). We are not persuaded.

For a summary exhibit to be admissible under Federal Rule of Evidence 1006, courts generally require that (1) the underlying document is so voluminous as to make comprehension difficult and inconvenient, although not necessarily literally impossible; (2) the underlying document itself must be admissible, although the offering party need not actually enter them; (3) the party introducing the chart must make the underlying documents reasonably available for inspection and copying; and (4) the chart must be accurate and nonprejudicial. *See, e.g.*, *United States v. Hemphill*, 514 F.3d 1350, 1359 (D.C. Cir. 2008).

Patent Owner argues that Exhibits 2108–2114 and 2120–2122 condense a large amount of data. Paper 72, 6. In addition, Patent Owner represents, and Petitioner does not dispute, that Patent Owner has made the underlying IMS data available to Petitioner for inspection and copying. *Id.* at 3. The fact that the underlying IMS data are not of record in this case does not justify the exclusion of these exhibits. Indeed, Federal Rule of Evidence 1006 mandates not that the underlying document be admitted, but only it is admissible. Here, Petitioner does not contend that the underlying IMS data is inadmissible.

Petitioner argues that "because the IMS data is not of record in this proceeding, neither the Petitioners nor the Board can test the accuracy of the summaries prepared by Dr. Grabowski." Paper 69, 4. But, when federal courts admitted compiled evidence without also admitting the underlying document, they similarly could not have verified the accuracy of the summaries. In addition, because Patent Owner has made the IMS data

available to Petitioner, Petitioner was able, if it so chose, to ascertain the accuracy of the summaries.

Because Patent Owner has satisfied the requirements for admitting summaries compiled under Federal Rule of Evidence 1006, we deny Petitioner's Motion to Exclude as to Exhibits 2108–2114 and 2120–2122.

Petitioner argues that in paragraphs 13, 14, 16, 17, 19, 26–32, 39, and 41–45 of his Declaration, Dr. Grabowski relies on Exhibits 2108–2114 and 2120–2122. *Id.* at 4–6. Because those exhibits should be excluded, Petitioner asserts, the expert testimony based thereon should also be excluded. *Id.* As explained above, we decline to exclude Exhibits 2108–2114 and 2120–2122. Thus, we also decline to exclude Dr. Grabowski's testimony based on those exhibits.

According to Petitioner, Exhibits 2115–2119 each represent a single page of a document titled "Mid-Year Tracker." Paper 69, 6. Petitioner points out that the Mid-Year Tracker is at least 134 pages long, and Patent Owner only produced five pages in this case. *Id.* at 6–7. Petitioner asserts that under Federal Rule of Evidence 106, selective citation and reliance on excerpts from the Mid-Year Tracker is unfair and prejudicial. *Id.* at 7. We, again, are not persuaded.

Federal Rule of Evidence 106 provides that "[i]f a party introduces all or part of a writing or recorded statement, an adverse party may require the introduction, at that time, of any other part — or any other writing or recorded statement — that in fairness ought to be considered at the same time." As Patent Owner correctly points out, "Rule 106 does not prohibit admission of an incomplete document. Instead, it allows the party against

whom the document is introduced to place the remainder in evidence." Paper 72, 12 (quoting 1 *Weinstein on Evidence* § 106.02[1]).

Patent Owner represents, and Petitioner does not dispute, that Patent Owner has made the Mid-Year Tracker available to Petitioner and stated that Petitioner may use the document in this proceeding. *Id.* at 3–4. Thus, Petitioner was able, if it so chose, to ascertain the pages Patent Owner relies on are accurate. As a result, we agree with Patent Owner that neither Federal Rule of Evidence 106 nor the interest of justice requires us to exclude Exhibits 2115–2119. We deny Petitioner's Motion to Exclude in this regard.

Petitioner argues that in paragraphs 38 and 40–44 of his Declaration, Dr. Grabowski relies on Exhibits 2115–2119. Paper 69, 8–9. Because those exhibits should be excluded, Petitioner asserts, the expert testimony based thereon should also be excluded. *Id.* As explained above, we decline to exclude Exhibits 2115–2119. Thus, we also decline to exclude Dr. Grabowski's testimony based on those exhibits.

Petitioner further requests that we exclude paragraphs 15, 19–23, 37, and 50–56 of Grabowski Declaration because the documents cited in support thereof are not of record. *Id.* at 9–10. We find Petitioner's argument unpersuasive, again. Here, Dr. Grabowski appears to have relied on documents publicly available on the internet, and have provided the URLs for those documents. In addition, under Federal Rule of Evidence 703, an expert witness may rely on otherwise inadmissible evidence in forming his opinions. Thus, even though Petitioner is correct that Patent Owner did not produce the documents cited in these paragraphs of Grabowski Declaration, we decline to exclude Dr. Grabowski's testimony based on those documents.

IV. CONCLUSION

We conclude that Petitioner has shown by a preponderance of the evidence that claims 1–20 of the ’250 patent are unpatentable.

V. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that claims 1–20 of the ’250 patent are held unpatentable;

FURTHER ORDERED that Patent Owner’s Motion to Exclude Evidence is *denied-in-part and dismissed-in-part as moot*;

FURTHER ORDERED that Petitioner’s Motion to Exclude Evidence is *denied*; and

FURTHER ORDERED that, because this is a Final Written Decision, the 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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