United States Court of Appeals for the Federal Circuit

YEDA RESEARCH AND DEVELOPMENT CO., LTD.,
Appellant

v.

MYLAN PHARMACEUTICALS INC., AMNEAL PHARMACEUTICALS LLC,
Appellees

2017-1594, 2017-1595, 2017-1596

Appeals from the United States Patent and Trademark Office, Patent Trial and Appeal Board in Nos. IPR2015-00643, IPR2015-00644, IPR2015-00830, IPR2015-01976, IPR2015-01980, IPR2015-01981.

Decided: October 12, 2018

WILLIAM M. JAY, Goodwin Procter LLP, Washington, DC, argued for appellant. Also represented by WILLIAM G. JAMES, II; ELIZABETH HOLLAND, New York, NY; DARYL L. WIESEN, Boston, MA; JOHN C. O'QUINN, Kirkland & Ellis LLP, Washington, DC; LESLIE M. SCHMIDT, New York, NY.

DAVID LEE ANSTAETT, Perkins Coie, LLP, Madison, WI, argued for appellees. Appellee Mylan Pharmaceuticals Inc. also represented by SHANNON BLOODWORTH, ROBERT SWANSON, BRANDON MICHAEL WHITE, Washington, DC; DAN L. BAGATELL, Hanover, NH; CHRISTINA JORDAN MCCULLOUGH, Seattle, WA.

ANTHONY JAMES FITZPATRICK, Duane Morris LLP, Boston, MA, for appellee Amneal Pharmaceuticals LLC. Also represented by VINCENT CAPUANO, CHRISTOPHER S. KROON; PATRICK GALLAGHER, Boca Raton, FL.

Before REYNA, BRYSON, and STOLL, *Circuit Judges*.

REYNA, *Circuit Judge*.

In this consolidated appeal, Appellant Yeda Research & Development Co., Ltd. challenges the Patent Trial and Appeal Board's final written decisions finding the claims of U.S. Patent Nos. 8,232,250, 8,399,413, and 8,969,302 unpatentable as obvious in three *inter partes* review proceedings. We affirm the Board's decisions.[1]

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[1] In a companion case decided today, *Teva Pharmaceuticals USA, Inc. v. Sandoz Inc.*, No. 17-1575 (Fed. Cir. Oct. 12, 2018), Teva Pharmaceuticals USA, Inc., Teva Pharmaceutical Industries, Ltd., Teva Neuroscience, Inc., and Yeda Research and Development Co., Ltd., appeal the decision of the United States District Court for the District of Delaware invalidating all asserted claims of U.S. Patent Nos. 8,232,250, 8,399,413, 8,969,302, and 9,155,776.

BACKGROUND

I. Patents at Issue

Yeda Research and Development Co., Ltd. ("Yeda") is the assignee of U.S. Patents Nos. 8,232,250, 8,399,413, and 8,969,302 (the '250, '413, and '302 patents, respectively), all entitled "Low Frequency Glatiramer Acetate Therapy." The patents, collectively referred to as the "Copaxone patents," share a common specification and claim priority to the same two provisional applications. *See* J.A. 267, 279, 291. The earliest priority date of the Copaxone patents is August 20, 2009. *Id.*

The Copaxone patents describe and claim COPAXONE® 40mg/mL, a treatment for relapsing-remitting multiple sclerosis ("RRMS"). RRMS is a form of multiple sclerosis, an autoimmune disorder that causes the body's immune system to attack the central nervous system. RRMS is characterized by unpredictable relapses followed by periods of remission with no new signs of disease activity.

The active ingredient in COPAXONE® 40mg/mL is glatiramer acetate ("GA"), a synthetic mixture of polypeptides. GA is also known as "copolymer 1" or "Cop. 1." COPAXONE® 40mg/mL is supplied as a single-dose prefilled syringe. Broadly, the treatment consists of the injection of 40mg of GA three times a week, abbreviated "40mg GA 3x/week." Relevant to this appeal, side effects of GA injections include injection-site reactions ("ISRs") and immediate post-injection reactions ("IPIRs"). ISRs are physical symptoms at the injection site, such as swelling or itchiness. IPIRs are reactions immediately following an injection, such as flushes, sweating, or palpitations.

Prior to COPAXONE® 40mg/mL, in 1996 the Food and Drug Administration ("FDA") approved

COPAXONE® 20mg/mL, a regimen consisting of the daily injection of 20mg GA. Daily GA injections were known to subject patients to discomfort, including side effects in the form of ISRs and IPIRs. J.A. 6956.

For analyzing the obviousness of the Copaxone patents, a key limitation of the claims is the administration of a 40mg GA dose in three subcutaneous injections over seven days. Claim 1 of the '250 patent is representative:

> 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.

'250 patent col. 16 ll. 35–45.

Certain claims of the '250 and '413 patents further require improved tolerability and/or reduced frequency of injection reactions in the claimed regimen as compared to 20mg daily. '250 patent col. 17 l. 24–col. 18 l. 6; '413 patent col. 16 ll. 51–54.

Apart from claim 1 of the '302 patent, all independent claims require at least one day between doses. '250 patent col. 16 ll. 35–45, col. 17 l. 25–col. 18 l. 6, col. 18 ll. 19–26; '413 patent col. 16 ll. 26–36, col. 18 ll. 1–13, col. 18 ll. 14–28; '302 patent col. 17 ll. 4–12. Claim 1 of the '302 patent does not specify any

particular interval between doses, but dependent claims 4 and 5 limit injections to certain combinations of days of the week, all with at least one day between injections, and independent claim 10 of the '302 patent requires that the injection be administered "three times per week with at least one day between every subcutaneous injection." '302 patent col. 16 ll. 37–41, col. 16 ll. 47–58, col. 17 ll. 4–12.

II. Prior Art References

The first clinical trial for using GA to treat multiple sclerosis was in 1987 by Dr. Bornstein et al. ("Bornstein"),[2] which was followed later by a Teva Phase III clinical trial in 1995. Both Bornstein and the Phase III trial tested 20mg GA daily. J.A. 7279–80, 7282–85, 6895–7235. The 20mg/day dose was selected without performing conventional optimal-dose-finding studies. J.A. 7239.

The Bornstein study showed that GA administered subcutaneously for two years at a daily dose of 20mg "produced clinically important and statistically significant beneficial effects." J.A. 7284. Participants in both Bornstein and the Phase III trial reported ISRs and IPIRs as side effects. J.A. 7284, 6934. The Phase III trial noted "adverse experience" as the main reason contributing to patient dropout, and "[t]he most common adverse event associated with dropout was injection site reaction." J.A. 6934. A Phase III trial reviewer made recommendations for future researchers to explore dose-response and dose-ranging studies, asking "Is 20 mg the optimum dose? Are daily injections necessary?" J.A. 6956.

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[2] Murray B. Bornstein et al., *A Pilot Trial of COP 1 in Exacerbating-Remitting Multiple Sclerosis*, 317 New Eng. J. Med. 408, 408–14 (1987).

In 1996, following both Bornstein and the Phase III clinical trial, FDA approved Teva's New Drug Application ("NDA") for COPAXONE® 20mg, 20mg GA injected daily. In its 1996 Summary Basis of Approval ("SBOA"), the FDA recommended that Teva "evaluate the necessity of daily [GA] injections as opposed to more infrequent intermittent administration of the drug" because the daily dosing regimen "seems like it would subject the patient to an excessive amount of discomfort if it is not necessary to maintain efficacy." J.A. 7146.

A 2002 study by Flechter et al.[3] ("Flechter") evaluated the treatment of RRMS with 20mg of GA administered every other day. J.A. 7236–40. Flechter concluded 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." J.A. 7240. Flechter also noted that patient dropout rates decreased when GA was administered every other day as opposed to daily. J.A. 7240 ("It should be stressed that the dropout rate was lower in the alternate-day group than in the daily-injection regime (39.7% versus 60.3%, $p < 0.01$).").

A prior art patent application, International Patent Application No. WO 2007/081975, *Method of Treating Multiple Sclerosis* ("Pinchasi"), was published in 2007. J.A. 6857–88. Pinchasi discloses a 40mg GA, every other day dosing regimen for the treatment of RRMS. Pinchasi cites to the data from

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[3] Shlomo Flechter et al., *Copolymer 1 (Glatiramer Acetate) in Relapsing Forms of Multiple Sclerosis: Open Multicenter Study of Alternate-Day Administration*, 25 Clinical Neuropharmacology 11, 11–15 (2002).

Cohen, another GA study, to conclude that "[t]he 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." J.A. 6876.

III. State of the Art Reference

There is an additional reference relevant to this appeal, a 2009 study by Omar Khan[4] ("Khan 2009"). J.A. 9331–32. Khan 2009 was published three weeks after August 20, 2009, the priority date of the asserted patents, and thus does not qualify as statutory prior art, but the study began two years earlier. J.A. 9331–32. The study abstract noted that "[t]here is considerable interest in studying a more patient friendly dosing regimen of GA that may be as efficacious and better tolerated than daily GA." J.A. 9331. Following the results of an earlier study, Khan 2008, showing that alternate day administration of GA appears to be as effective as daily administration, Khan 2009 compared 20mg GA administered twice a week to 20mg GA administered daily in a pilot, prospective, randomized, and rater-blinded two-year study. J.A. 9331; *see infra* note 8.

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[4] O. Khan et al., *Glatiramer Acetate 20mg Subcutaneous Twice-Weekly Versus Daily Injections: Results of a Pilot, Prospective, Randomised, and Rater-Blinded Clinical and MRI 2-Year Study in Relapsing-Remitting Multiple Sclerosis*, 15 Multiple Sclerosis S249, S249–50 (2009).

IV. Proceedings before the Board

Mylan Pharmaceuticals, Inc. ("Mylan") filed petitions for *inter partes* review ("IPR") in IPR2015-00643, IPR2015-00644, and IPR2015-00830, challenging all claims of the '250, '413, and '302 patents, respectively, on grounds pursuant to 35 U.S.C. §§ 102 and 103. The Patent Trial and Appeal Board (the "Board") instituted review of all claims of the Copaxone patents on two grounds: obviousness over Pinchasi in view of FDA's 1996 SBOA, and over Pinchasi in view of Flechter.[5] J.A. 644 (instituting

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[5] In each of its Institution Decisions, the Board instituted on all claims but less than all grounds petitioned. *See* J.A. 644, 1720–21, 2710–11. The Supreme Court held in *SAS Institute Inc. v. Iancu* that if the Director institutes IPR proceedings, the Board's review must proceed "'[i]n accordance with' or 'in conformance to' the petition," including "'each claim challenged' and 'the grounds on which the challenge to each claim is based.'" 138 S. Ct. 1348, 1355–56 (2018) (alteration in original). Post-*SAS*, this court has held that remand to the Board can be appropriate to consider non-instituted grounds as well as non-instituted claims. *See BioDelivery Scis. Int'l, Inc. v. Aquestive Therapeutics, Inc.*, 898 F.3d 1205, 1208 (Fed. Cir. 2018) (collecting cases).

At oral argument, Mylan stated that it did not seek remand on the grounds of partial institution in light of the Supreme Court's decision in *SAS*. Oral Arg. at 6:12–7:05 (May 1, 2018), *available at* http://oralarguments.cafc.uscourts.gov/default.aspx?fl=2017-1594.mp3. In the absence of a request for relief on the basis of *SAS*, we are not sua sponte obliged to act on the *SAS* error in this case. *See PGS*

IPR on the '250 patent), 1720–21 ('413 patent), 2710–11 ('302 patent). Subsequently, Amneal Pharmaceuticals LLC filed for each patent substantially identical petitions to those already filed by Mylan, and moved to join Mylan's proceedings. The Board subsequently consolidated Amneal Pharmaceuticals' petitions with those already filed by Mylan. J.A. 894–898, 1970–74, 3489–95. Amneal Pharmaceuticals and Mylan are collectively referred to as "Petitioners."

The Board's analysis of the independent claims was similar for all three patents. The Board first noted that Pinchasi discloses every limitation of the independent claims of the Copaxone patents, except for the dosing regimen of three doses per seven day period. The Board found that a person of ordinary skill in the art ("POSITA") would have been motivated to use a 40mg dose, crediting the testimony of Petitioners' expert, Dr. Green, who noted that Pinchasi demonstrated increased efficacy of 40mg GA compared to 20mg with no significant difference in side effects, and citing Cohen,[6] a study which con-

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Geophysical AS v. Iancu, 891 F.3d 1354, 1362–63 (Fed. Cir. 2018).

[6] J.A. Cohen et al., *Randomized, Double-Blind, Dose-Comparison Study of Glatiramer Acetate in Relapsing-Remitting MS*, 68 Neurology 939, 939–44 (2007).

Cohen, published in 2007, was a "Randomized, double-blind, dose-comparison study of glatiramer acetate in relapsing-remitting MS." J.A. 6889–94. Cohen compared daily subcutaneous injections of 20mg and 40mg GA dosages, and concluded that the 40mg dose may be "more effective" than the 20mg dose "in reducing MRI activity and clinical relapses." J.A. 6889. Cohen also noted that the onset of action

cluded that daily administration of 40mg GA was effective, safe, and well tolerated. In reaching this finding, the Board also found that FORTE,[7] a phase III clinical trial comparing 40mg GA and 20mg GA, would not have taught away from using 40mg because it did not criticize, discredit, or discourage the 40mg GA dose.

The Board next considered whether there was a motivation to modify Pinchasi's 40mg every other day

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of the 40mg dose is more rapid compared to 20mg. J.A. 6894. ISRs were the most frequent adverse event for both doses, occurring at roughly equal rates. J.A. 6892–93. IPIRs occurred more frequently in the 40mg group than the 20mg group. J.A. 6892–93. Cohen thus concluded that the overall safety and side effect profile of the 40mg GA dose was "similar" to the 20mg dose, but "was associated with a greater incidence of certain adverse effects." J.A. 6894.

[7] Giancarlo Comi, Jeffrey A. Cohen, Massimo Filippi for the FORTE Study Group, *Results from a Phase III, One-Year, Randomized, Double-Blind, Parallel-Group, Dose-Comparison Study with Glatiramer Acetate in Relapsing-Remitting Multiple Sclerosis*, 14 Multiple Sclerosis S299, S299–S301 (2008); J.A. 11532–40.

The FORTE study evaluated the safety, tolerability, and efficacy of 40mg GA compared to 20mg GA, and concluded that there are "[n]o significant differences in efficacy measures between GA 20mg and GA 40mg," and that the 40mg dose has a "[g]ood safety and tolerability profile" with "no unexpected adverse effect with the high dose." J.A 11532–40. FORTE also confirmed a finding from an earlier study, Cohen, that the 40mg dose provides an earlier onset of action. J.A. 11540.

regimen. The Board noted that the difference between the challenged claims (6 doses over 2 weeks) and Pinchasi (7 doses over 2 weeks) was only one less injection every two weeks. The Board then found motivation to eliminate one injection every other week to increase patient compliance, relying in part on Petitioners' expert Dr. Green, who testified that decreasing the frequency of injections helps with patient adherence to a treatment regimen, and FDA's 1996 SBOA, which recommended that the necessity of daily injections, as opposed to less frequent administration, be evaluated. The Board further relied on other prior art references, including Flechter, Khan 2008,[8] and Caon,[9] which showed that alternate-day

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[8] Omar 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, S296 (2008).

This 2008 study by Omar Khan and others ("Khan 2008") compared the effect of daily versus every other day administration of 20mg GA subcutaneous injections for the treatment of RRMS. J.A. 7252. The study abstract noted that although the recommended dose for treating RRMS is daily 20mg GA injections, "the optimal dose remains unknown" and there is "considerable interest in alternate dosing regimens of GA" because daily injections "can be challenging for long-term patient compliance." J.A. 7252. Thirty patients were randomly assigned to receive 20mg GA dosed daily or every other day. After two years, there were "no differences" between the two groups in relapse rate or disease progression. J.A. 7252. Additionally, after the first two years elapsed, patients in each group were given the option to continue or

dosing of 20mg was safe, well-tolerated, as effective as daily 20mg, reduced injection reactions, and that patients in the daily-injection group preferred less frequent dosing. The Board also found Khan 2009 probative of the fact that POSITAs were motivated to investigate dosing regimens of GA with fewer injections to improve patient compliance.

Having found a motivation in the prior art to pursue a less frequent dosing regimen, the Board found that a POSITA would have a reasonable expectation of success in administering 40mg GA three times per week in light of testimony that GA was "a forgiving drug," and that combining a 40mg dose with three-times-a-week administration produced a weekly dose virtually identical to the FDA-approved regimen of 20mg GA daily. The Board then concluded that, in light of the evidence presented, a POSITA would have had a reason to modify Pinchasi's dosing regimen of 40mg GA every other day to 40mg GA 3x/week, thus

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switch groups, and were monitored for an additional two years. Every patient in the daily group opted to switch to every other day administration. After four years, there was no difference between the crossover group and the group that was always dosed every other day.

[9] Christina 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 (Suppl. 3) A317 (2009).

The Caon reference, published in 2009, reports the same data from the Khan 2008 study, but further noted that "[i]njection related lipoatrophy was significantly less" in the every other day group. J.A. 7253.

rendering the claimed 40mg 3x/week limitation obvious.

The Board also considered additional limitations for each patent, including limitations requiring improved tolerability, reduced frequency of adverse reactions, and specific injection schedules, and also found them obvious in light of the prior art. With regard to the objective indicia of nonobviousness, the Board concluded that the objective indicia were insufficient to overcome the primary findings of obviousness. And finally, for similar but less detailed reasons as for Pinchasi/SBOA, the Board concluded that the claims are unpatentable over the combination of Pinchasi and Flechter.

Yeda moved for rehearing. The Board issued revised final written decisions that reached the same results. *Mylan Pharm. Inc. v. Yeda Research & Dev. Co.*, IPR2015-00643, No. 90, at 40 (P.T.A.B. Dec. 2, 2016) ("*'250 patent FWD*"); *Mylan Pharm. Inc. v. Yeda Research & Dev. Co.*, IPR2015-00644, No. 91, at 41 (P.T.A.B. Dec. 2, 2016) ("*'413 patent FWD*"); *Mylan Pharm. Inc. v. Yeda Research & Dev. Co.*, IPR2015-00830, No. 85, at 37 (P.T.A.B. Dec. 2, 2016) ("*'302 patent FWD*"). Yeda appeals the Board's reliance on Khan 2009 and its obviousness decisions. We have jurisdiction pursuant to 28 U.S.C. § 1295(a)(4)(A).

DISCUSSION

We review decisions of the Board under the standard of the Administrative Procedure Act (APA). *Novartis AG v. Torrent Pharm. Ltd.*, 853 F.3d 1316, 1323 (Fed. Cir. 2017). We hold unlawful and set aside the actions of the Board if they are "not in accordance with law" or "unsupported by substantial evidence." 5 U.S.C. § 706.

I. Khan 2009

Yeda contends that its due process rights and the APA were violated because it did not have notice of, and an opportunity to respond to, Khan 2009. Yeda also argues that the Board violated 35 U.S.C. § 311(b) by relying on Khan 2009, which does not qualify as statutory prior art.

Khan 2009 was first introduced as part of the reply declaration of Dr. Green, Petitioners' expert. In its patent owner response, Yeda had argued that, as of the priority date, a POSITA would have believed that more frequent than daily administrations of GA would have been the best way to enhance efficacy. J.A. 758. In his reply declaration, Dr. Green responded that "[n]umerous prior art references suggested further investigation of less frequent dosing regimens prior to 2009." J.A. 9529 ¶ 29. After citing other prior art references, namely the SBOA, Flechter, Khan 2008, and Caon, Dr. Green discussed Khan 2009, noting that "before the priority date, POSAs had completed a clinical trial investigating 20 mg administered twice weekly, for a total weekly dose of only 40 mg." J.A. 9532 ¶ 32. Dr. Green concluded that "the Khan 2009 reference demonstrates that—counter to what Patent Owner claims—POSAs were motivated before the priority date to explore less frequent alternative dosing regimens." J.A. 9532–33 ¶ 32.

We first consider whether Yeda's due process rights were violated. "[T]he introduction of new evidence in the course of the trial is to be expected in *inter partes* review trial proceedings and, as long as the opposing party is given notice of the evidence and an opportunity to respond to it, the introduction of such evidence is perfectly permissible under the APA." *Genzyme Therapeutic Prods. LP v. Biomarin*

Pharm. Inc., 825 F.3d 1360, 1366 (Fed. Cir. 2016). Here, Yeda received notice of Khan 2009 in Dr. Green's reply declaration, attached to Petitioners' reply. Yeda deposed Dr. Green after receiving his reply declaration; he discussed Khan 2009 in that deposition and was questioned about it. J.A. 11164–65, 11176–79. Yeda also moved to exclude Khan 2009 as irrelevant, which the Board denied. J.A. 1153–54; *see also '250 patent FWD*, at 35–36. Yeda could have, but did not, address Khan 2009 at the oral hearing or seek leave to file a surreply to substantively respond to Khan 2009, as encouraged by our precedent. *See Genzyme*, 825 F.3d at 1368.

Based on this record, Yeda received proper notice of and an opportunity to respond to Khan 2009—an opportunity Yeda took advantage of when it moved to exclude the study. But Yeda contends that it had no notice that the Board "might rely extensively" on Khan 2009 and make it "an essential part of its obviousness analysis." Appellant's Reply Br. 27. Thus, although Yeda frames its argument as being about due process, it really only challenges the Board's use of Khan 2009.

In its final written decisions, the Board acknowledged that Khan 2009 does not qualify as statutory prior art, but because the study began two years before the priority date of the Copaxone patents, the Board concluded 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." *'250 patent FWD*, at 15; *see also '413 patent FWD*, at 17; *'302 patent FWD*, at 16. With one exception, discussed below, the Board's use of Khan 2009 falls squarely within this stated purpose of providing evidence of the motivation of a POSITA to explore less frequent dosing regimens as of the priority date. *See '250*

patent FWD, at 15, 18, 36; *'413 patent FWD*, at 16–17, 19; *'302 patent FWD*, at 16, 18.

Yeda contends that the Board relied on Khan 2009 to supplement gaps in the prior art in violation of 35 U.S.C. § 311(b). Section 311(b) provides that the Board may consider the patentability of challenged claims "only on the basis of prior art consisting of patents or printed publications." We note that, before the Board, Yeda only sought to exclude Khan 2009 on the ground that it was irrelevant, and thus its argument regarding § 311(b) is arguably waived. J.A. 1153–54. However, § 311(b) is unrelated to the question of whether the Board's reliance on Khan 2009 was proper. While Khan 2009 indisputably does not qualify as prior art, § 311(b) only addresses prior art and is silent on the question of other evidence. The question before us, therefore, is whether the Board may consider non-prior art evidence, such as Khan 2009, in considering the knowledge, motivations, and expectations of a POSITA regarding the prior art.

Based on the statutory scheme, the PTO's own regulations, and prior Board decisions, the Board can rely on evidence other than just prior art. The statute permits IPR petitioners to rely on evidence beyond the asserted prior art. Section 312(a)(3) of Title 35 specifies that a petition should include both "copies of patents and printed publications that the petitioner relies upon," and "affidavits or declarations of *supporting evidence and opinions*." So do the regulations. *See* 37 C.F.R. § 42.104(b) (describing the content of the petition, including both "the patents or printed publications relied upon for each ground," and "supporting evidence relied upon to support the challenge"). The Board has recognized that non-prior art evidence of what was known "cannot be applied, independently, as teachings separately combinable" with other prior art, but "can be relied on for their

proper supporting roles, e.g., indicating the level of ordinary skill in the art, what certain terms would mean to one with ordinary skill in the art, and how one with ordinary skill in the art would have understood a prior art disclosure." *Dominion Dealer Sols., LLC v. AutoAlert, Inc.*, IPR2014-00684, 2014 WL 5035359, at *5 (P.T.A.B. Oct. 6, 2014).

In this regard, Dr. Green's reliance on Khan 2009 is permissible, as it supports and explains his position that a POSITA would have thought less frequent dosing worthy of investigation as of the priority date. We note that Dr. Green also relied on multiple prior art references—namely the SBOA, Flechter, Khan 2008, and Caon—in support of this opinion. J.A. 9532 ¶ 32. With one exception, the Board's use of Khan 2009 is in line with Dr. Green's narrow interpretation, and does not constitute error. *See '250 patent FWD*, at 15 ("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."); *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.'" (emphasis added)); *id.* at 18 (mentioning Khan 2009 as one of many studies of less frequent dosing, undermining the opinion of Yeda's expert that a POSA would want to administer more than once daily)[10]; *id.* at 35 ("[Khan 2009] reflects that, before

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[10] We recognize that, in this instance, the Board included Khan 2009 at the end of a string citation listing "[n]umerous *prior art references* studying less frequent dosing." *'250 patent FWD*, at 18 (emphasis added); *'413 patent FWD*, at 18 (same); *'302 patent FWD*, at 18 (same). Having considered the Board's

the '250 patent invention, those skilled in the art were motivated to investigate dosing regimens with less frequent than daily injections"); *'413 patent FWD*, at 16–17 (same as *'250 patent FWD*, at 15); *'302 patent FWD*, at 16 (same).

In one instance, the Board relied on Khan 2009 for a different purpose, namely, in deciding whether a POSITA would have had a reasonable expectation of success of a thrice-weekly regimen. *'250 patent FWD*, at 21 ("[A]s 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."). To the extent that this reliance was error, we conclude that it was harmless error. Khan 2009 was the last piece of evidence in a lengthy analysis, in which the Board also relied on Flechter, Khan 2008, Caon, Pinchasi, and testimony from Dr. Green in finding a POSITA would have had a reasonable expectation of success in the claimed regimen. Even if the Board's reliance on Khan 2009 was improper, it is harmless error because substantial evidence otherwise supports the Board's conclusion.

II. Obviousness under 35 U.S.C. § 103

Under 35 U.S.C. § 103(a), a patent may not be obtained "if the differences between the subject matter

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decision as a whole, and in particular the portion discussing how Khan 2009 is not statutory prior art, *'250 patent FWD*, at 15–16, we conclude that the Board's characterization of Khan 2009 as being prior art was a simple oversight, constituting harmless error.

sought to be patented 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." 35 U.S.C. § 103(a) (2006).[11]

Obviousness is a question of law with underlying factual findings relating to the scope and content of the prior art; the differences between the claims and the prior art; the level of ordinary skill in the pertinent art; and any secondary considerations of nonobviousness. *ZUP, LLC v. Nash Mfg., Inc.*, 896 F.3d 1365, 1371 (Fed. Cir. 2018) (citing *Graham v. John Deere Co. of Kan. City*, 383 U.S. 1, 17–18 (1966)). The inherent teaching of a prior art reference is a question of fact. *Par Pharm., Inc. v. TWi Pharm., Inc.*, 773 F.3d 1186, 1194 (Fed. Cir. 2014).

On appeal, Yeda disputes the Board's conclusion that the 40mg GA 3x/week dosing regimen disclosed in the Copaxone patents would have been obvious to a person of skill in the art. Yeda also appeals the invalidation of the '250 patent's claims relating to increased tolerability, the '413 patent's claims relating to decreased frequency of side effects, and the '302 patent's claims relating to specific-day dosing regi-

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[11] Congress amended § 103 when it passed the Leahy-Smith America Invents Act (AIA). Pub. L. No. 112–29, § 3(c), 125 Stat. 284, 287 (2011). Because the applications that led to the patents at issue have never contained a claim having an effective filing date on or after March 16, 2013 (the effective date of the statutory changes enacted in 2011), or a reference under 35 U.S.C. §§ 120, 121, or 365(c) to any patent or application that ever contained such a claim, the pre-AIA § 103 applies. *Id.* § 3(n)(1), 125 Stat. at 293.

mens. Yeda does not appeal on the objective indicia of nonobviousness. We address each argument in turn.

A. 40mg GA 3x/week Dosing Regimen

Yeda contends that the Board erred as a matter of law in finding the claimed 40mg GA 3x/week dosing regimen obvious. Specifically, Yeda claims that, in finding that a POSITA had a reasonable expectation of success, the Board disregarded inherent uncertainties associated with GA. Yeda also argues that the Board engaged in hindsight bias, considered the obviousness of individual claim elements separately rather than the claimed invention as a whole, and failed to account for the "minimum effective dose" principle in considering what the prior art taught POSITAs.

We first consider Yeda's argument that the Board erred as a matter of law in finding a reasonable expectation of success of the claimed regimen by disregarding certain uncertainties associated with GA, namely the fact that GA's pharmacokinetic and pharmacodynamic ("pk/pd") profile, mechanism of action, optimal dose, and active species are all unknown. Yeda contends that this case is "indistinguishable" from *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litigation*, 676 F.3d 1063 (Fed. Cir. 2012), and argues that a reasonable expectation of success is categorically impossible in the absence of a pk/pd profile. Appellant's Opening Br. 38–39.

In *Cyclobenzaprine*, we held that bioequivalence alone could not establish obviousness because "skilled artisans could not predict whether any particular PK profile, including a bioequivalent one, would produce a therapeutically effective formulation." 676 F.3d at 1070. The court applied traditional motivation and reasonable-expectation-of-success analysis, reasoning

that "[w]hile it may have been obvious to experiment with the use of the same PK profile [from an immediate-release formulation] when contemplating an extended-release formulation, there [wa]s nothing to indicate that a skilled artisan would have had a reasonable expectation that such an experiment would succeed in being therapeutically effective." *Id.* In *Cyclobenzaprine*, there were no prior art clinical studies to suggest what would be a therapeutically effective formulation.

We do not read *Cyclobenzaprine* as establishing a rigid rule categorically precluding obviousness determinations without pk/pd data. There, the court's error was relying on bioequivalence alone, without any evidence in the prior art teaching or suggesting a therapeutically effective formulation to one skilled in the art, such as pk/pd data. Here, however, the Board committed no such error; the record is replete with prior art that would have taught or suggested a therapeutically effective formulation to a POSITA. The Board pointed to clinical studies that taught the effectiveness of 20mg daily (Copaxone® 20mg), 20mg every other day (Flechter, Khan 2008, Caon), and 40mg daily (Cohen, FORTE), and the Pinchasi application, which suggested that 40mg every other day would be therapeutically effective. *See '250 patent FWD*, at 12–14, 20; *'413 patent FWD*, at 16–18, 21–22; *'302 patent FWD*, at 15–16, 20, 29–30.

Further, the evidence considered by the Board reveals that pk/pd data was largely irrelevant to the invention. The Board credited testimony from Petitioners' expert Dr. Green, who testified that POSITAs considered GA to be a "forgiving drug," with a wide range of likely efficacious doses. *E.g.*, *'250 patent FWD*, at 16–17. Yeda itself argued to the Board that the "plasma half-life of GA . . . is irrelevant to the pharmaceutical effect of the drug," and that "GA

cannot be measured in the plasma and no PK/PD correlation is even possible." J.A. 772 (citation omitted). In light of Yeda's own representations to the Board that "the standard small molecule textbook pharmacokinetic principles . . . cannot be used to predict the therapeutic effects of GA," *id.*, we decline to find error in the Board's obviousness decision simply because it lacked pk/pd data.

Yeda makes challenges to the Board's factual findings concerning reasonable expectation of success, none of which we find persuasive. Although Yeda contests the Board's finding that GA is a "forgiving drug," leading POSITAs to have a reasonable expectation in administering 40mg GA 3x/week, this conclusion is supported by substantial evidence, including Dr. Green's expert testimony. *'250 patent FWD*, at 18–19. The Board's finding that the uncertainty around GA's mechanism of action would motivate a POSITA to stick to dosing regimens with existing clinical support, such as 20mg and 40mg, is supported by substantial evidence from Dr. Green. *Id.* at 18. Because "the expectation of success need only be reasonable, not absolute," we find no error in these findings. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007).

Next, Yeda argues that the Board improperly considered the claimed dose amount and the claimed frequency separately, "manipulat[ing] both parameters at the same time," without finding an affirmative reason to combine them. Appellant's Opening Br. 45, 48. We disagree. The Board's analysis began with Pinchasi, which it found disclosed every claim element except the requirement to inject 40mg GA 3x/week, as opposed to every other day. *'250 patent FWD*, at 10. The only difference between the prior art and the claimed invention was, therefore, the difference between thrice weekly and every other day

administration. We do not read the Board's decision as manipulating both parameters simultaneously, but rather, as considering the claimed regimen in the context of the prior art regimens, both in terms of dose size and frequency.

Nor do we find, as Yeda urges, that the Board improperly engaged in hindsight by starting its analysis with Pinchasi as the closest prior art reference. Appellant's Reply Br. 3–4. At the outset, we note that this argument was raised by Yeda for the first time in its reply brief, and thus is waived. And while we have previously cautioned against relying on hindsight bias in selecting a lead prior art reference after the fact, we find no hindsight in the Board's analysis. *See, e.g.*, *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1337 (Fed. Cir. 2016) ("The real question is whether that skilled artisan would have plucked one reference out of the sea of prior art . . . ."); *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008). Here, far from a "sea of prior art," the references before the Board presented a finite and known pool of dose and frequency options easily traversed to show obviousness. *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007) ("When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp."). The dosages in the prior art that had clinical support for being effective and safe consisted of only two: 20mg and 40mg. The prior art disclosed both daily and every other day administration, and the Board found a motivation for both less frequent injections and a thrice-weekly regimen specifically. *'250 patent FWD*, at 13–16. Given the small field of prior art references with clinical support, we find no clear error in the Board's finding that the "[p]otent

and promising activity in the prior art" would have encouraged a POSITA to traverse the experimental options to produce this invention. *See Daiichi Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010); *Ortho-McNeil*, 520 F.3d at 1365.

The Board thoroughly addressed Yeda's arguments to the contrary, namely, that a POSITA would not use 40mg of GA on any dosing schedule, would not have used a 3x/week dosing regimen, and that there would not have been a reasonable expectation of success of 40mg GA 3x/week being therapeutically effective. *See '250 patent FWD*, at 11. In so doing, the Board found that a POSITA would have been motivated to use 40mg, *id.* at 11–13, that a POSITA would have been motivated to use a 3x/week dosing regimen, *id.* at 13–16, and that a POSITA would have had a reasonable expectation of success in using 40mg GA 3x/week to be therapeutically effective, *id.* at 16–22. Given these findings, and given that the difference between the claimed invention and the prior art is only one dose per two week period, the Board did not need to articulate a further motivation to combine the 40mg dose and the 3x/week schedule.

Yeda makes other arguments attacking the Board's fact finding regarding motivation to combine. For instance, Yeda points to Cohen, which reported a slightly higher rate of adverse effects in 40mg compared to 20mg doses, as evidence that a POSITA would not have been motivated to inject 40mg doses. However, the Board also considered the FORTE study, which noted that the higher 40mg dose "maintained the favorable safety and tolerability profile" of 20mg GA. *'250 patent FWD*, at 12–13. Yeda also contests Dr. Green's testimony relating to Rebif®, another RRMS drug that uses a 3x/week dosing regimen. Yeda argues that it was improper to rely on Rebif as proof of efficacy, in that GA and Rebif have

different mechanisms of action. However, Dr. Green did not rely on Rebif to demonstrate GA's efficacy, but rather for the point that patients adhered well to Rebif's regimen of thrice-weekly injections, suggesting that a 3x/week GA injection regimen would improve patient compliance. *Id.* at 16; J.A. 6628–29 ¶ 53. We have considered Yeda's other arguments to this effect and find them unpersuasive.

Finally, Yeda argues that the Board erred in failing to consider the "minimum effective dose" principle. According to Petitioners' expert, Dr. Peroutka, the minimum effective dose is the lowest dose of a drug that will achieve a desired effect, and in general, is preferred unless higher doses lead to increased efficacy with an acceptable amount of side effects. *Mylan Pharm. Inc. v. Yeda Research & Dev. Co.*, IPR2015-00643, Ex. 1003, ¶ 44 (P.T.A.B. Mar. 3, 2015) ("Peroutka Decl."). Based on this principle, Yeda argues that following the FORTE study—which concluded that the GA 40 mg dose did not demonstrate increased efficacy in reducing the relapse rate, J.A. 11308—a POSITA "would have had no motivation to pursue a 40mg dose, on any schedule." Appellant's Opening Br. 52. Yeda argues that the Board's failure to address minimum effective dose is legal error.

Although the Board did not address the minimum effective dose principle by name in its decisions, these omissions do not constitute reversible error. First, as an initial matter, the Board is "not require[d] . . . to address every argument raised by a party or explain every possible reason supporting its conclusion." *Synopsys, Inc. v. Mentor Graphics Corp.*, 814 F.3d 1309, 1322 (Fed. Cir. 2016), *overruled on other grounds by Aqua Prods., Inc. v. Matal*, 872 F.3d 1290, 1296 n.1 (Fed. Cir. 2017) (en banc). And while agencies are required to address "important aspect[s] of

the problem," *Motor Vehicle Mfrs. Ass'n of U.S., Inc. v. State Farm Mut. Auto Ins. Co.*, 463 U.S. 29, 43 (1983), here, minimum effective dose is mentioned only briefly in Yeda's patent owner responses, in a single paragraph discussing Petitioners' expert, Dr. Peroutka. *See* J.A. 752, 1828, 3365. As we have said numerous times, failure to explicitly discuss every fleeting reference or minor argument does not alone establish that the Board did not consider it. *See Novartis*, 853 F.3d at 1328 (citing cases).

Second, the record on appeal indicates that the Board considered the minimum effective dose principle. At oral argument, the Board discussed the effect of less frequent dosing on dose size. Yeda's counsel argued that, under the minimum effective dose principle, a POSITA would have "no reason to go to 40[mg]." J.A. 1352. In response, the Board queried whether, if a POSITA would have been motivated to move to less frequent dosing, "doesn't it open up the world of possibilities again that we can start with 20 and 40 and then start all over and figure out which is the proper less frequent dosing?" J.A. 1352; *see also* J.A. 1353–54. Further, Yeda's reliance on the minimum effective dose principle in its response was in support of its position that FORTE taught away from using 40mg. *See Mylan Pharm. Inc. v. Yeda Research & Dev. Co.*, IPR2015-00643, No. 26, at 17–19 (P.T.A.B. Nov. 20, 2015) (patent owner response) (discussing minimum effective dose under the subheading: "After the FORTE trial, a POSA would not have used a 40 mg dose of GA to treat MS"). The Board expressly addressed whether FORTE taught away from a 40mg dose in the final written decisions. *See, e.g.*, *'250 patent FWD*, at 13 ("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.").

In light of the foregoing, we conclude that substantial evidence supports the Board's reliance on the clinical data and its conclusion that a POSITA would be motivated to combine Pinchasi's 40mg every other day dose with a less frequent dosing regimen, such as 3x/week, and would have had a reasonable expectation of success in therapeutic effectiveness and patient compliance. Accordingly, we affirm the Board's finding that the 40mg GA 3x/week regimen is obvious in light of the prior art.

B. Increased Tolerability Claims

Claim 15 of the '250 patent, from which claims 16–18 depend, requires that the claimed 40mg GA 3x/week regimen improve tolerability as compared to the daily 20mg regimen. '250 patent col. 17 l. 24–col. 18 l. 6. In the '250 patent, "tolerability" "relates to the level of discomfort associated with GA treatment," and "is associated with the frequency and severity of post injection reactions and injection site reactions." *Id.* col. 7 ll. 33–37.

Yeda argues that the Board did not sufficiently address the tolerability limitations of claims 15–18 of the '250 patent. We disagree, and find that substantial evidence supports the Board's finding that a POSITA, considering the prior art teachings as a whole, had a reason to switch from 20mg GA daily to a 40mg GA 3x/week regimen, and would have known that doing so would increase the tolerability of the GA regimen as compared to 20mg GA daily. *'250 patent FWD*, at 25. The Board pointed to Khan 2008 and Caon, which reported that 20mg every other day had increased tolerability over 20mg daily, including significantly less lipoatrophy, as showing that every other day dosing decreases injection-related side effects. *Id.* at 24–25.

Yeda now claims that the Board disregarded other prior art references that contradict Khan 2008 and Caon, including Flechter and FORTE. Concerning Flechter, the Board concluded that Flechter does not show that every other day administration is less tolerable than daily administration. *Id.* at 33–34. This conclusion was based on the Board's rejection of testimony of Yeda's expert, Dr. Ziemssen, who compared Flechter with another study, Meiner, on the grounds that cross-study comparisons are not reliable. Having concluded elsewhere that Flechter makes no statement as to tolerability, there would be no reason for the Board to cite Flechter with respect to claims 15 to 18. And although FORTE was not cited in this section, the Board earlier in the decision noted FORTE's conclusion that the 40mg dose "maintained the favorable safety and tolerability profile of COPAXONE® 20mg." *Id.* at 13. Because the Board found that an increased dose does not decrease tolerability and the evidence reveals that a POSITA would believe that decreased injection frequency would increase tolerability, we conclude that the Board's decision is supported by substantial evidence and legally proper.

C. Reduced Frequency of ISRs and IPIRs Claims

Claim 7 of the '413 patent depends on claim 1, and further requires that the claimed method reduce the frequency of an IPIR or ISR relative to daily administration of 20 mg GA. '413 patent col. 16 ll. 51–54. The Board found all dependent claims of the '413 patent unpatentable as obvious in light of Pinchasi and the 1996 SBOA. *'413 patent FWD*, at 23–24.

In finding claim 7 obvious, the Board adopted the reasoning in Dr. Green's declaration discussing how

decreasing the frequency of injections decreases the frequency of reactions relative to 20mg daily. *Id.* at 23 (citing *Mylan Pharm. Inc. v. Yeda Research & Dev. Co.*, IPR2015-00644, Ex. 1004 ¶ 109 (Feb. 7, 2015) ("It would have been and is common sense that reducing the frequency of administration from 20 mg daily would in turn decrease the frequency of injection site reactions and immediate post injection reactions.")). The Board also considered, and rejected, Yeda's argument that 40mg doses are associated with more injection site reactions, on the grounds that it was not supported by the prior art. *Id.* at 24. Moreover, in the paragraph discussing claim 7, the Board cited portions of Petitioners' reply—which in turn relied on Khan 2008, Caon, Dr. Green's testimony, and other evidence—discussing how less frequent dosing would increase tolerability by reducing ISRs. *Id.* (citing J.A. 2117–20).

Yeda faults the Board for not considering all of its arguments. "[W]e will uphold a decision of less than ideal clarity if the agency's path may reasonably be discerned." *In re NuVasive, Inc.*, 842 F.3d 1376, 1383 (Fed. Cir. 2016) (quoting *Bowman Transp., Inc. v. Ark.-Best Freight Sys., Inc.*, 419 U.S. 281, 286 (1974)). Having reviewed the Board's decision, we conclude that while the Board's analysis regarding claim 7 is concise, it is supported by substantial evidence.

We are further convinced that the Board did not err because the record is replete with Board findings that increased tolerability claims would be obvious. As in the '250 patent, the '413 patent defines tolerability to be associated with the frequency of ISRs and IPIRs. '413 patent col. 7 ll. 28–32. And although claim 7 of the '413 patent does not itself reference tolerability, the parties and the Board referred to claim 7 as concerning tolerability. *See, e.g.*, J.A. 138 (Board's decision granting-in-part request for rehear-

ing) ("We note that none of the claims, other than claim 7, recite any limitation regarding tolerability."); J.A. 1371 (statement of Yeda's counsel at oral argument) ("One set of claims have to do with the increased tolerability of the GA treatment, and what I'm talking about now is '250, claims 14 to 17, and *'413, claim 7*." (emphasis added)). In light of the substantive overlap between the reduced frequency and the increased tolerability claims, and given our earlier holding that the Board did not err in finding the increased tolerability claims obvious, we affirm the Board's finding regarding claim 7 of the '413 patent. *See supra* Discussion, section II.B.

D. Specific Dosing Regimen Claims

Claims 4, 5, and 11 of the '302 patent each specify a particular three-day schedule in a seven-day period on which GA injections are administered. For example, claim 4 of the '302 patent requires that the three subcutaneous 40mg GA injections "are on three days each week selected from the group consisting of day 1, day 3 and day 5; day 1, day 3 and day 6; day 1, day 4 and day 6; day 2, day 4 and day 6; day 2, day 4 and day 7; [day] 2, day 5 and day 7; and day 3, day 5 and day 7." '302 patent col. 16 ll. 47–52.

In response to Yeda's argument that Pinchasi did not disclose all elements of these claims, the Board explained that the question is not whether Pinchasi discloses administering 40mg of GA three times weekly to meet the further limitations of claims 4, 5, and 11, but rather, "we must look at what the prior art teaches as a whole." *'302 patent FWD*, at 22. In considering these specific dosing regimen claims, the Board adopted the reasoning of Dr. Green in his expert declaration, namely that "[c]hoosing specific days each week, such as Monday, Wednesday, and Friday, for example" is obvious, and that "choosing

specific days for injections increases patient adherence and compliance." J.A. 6654 ¶ 107. The Board also adopted reasoning from the petition, including that "[t]he three specific days of the week are a matter of patient and physician choice from a limited number of possibilities." J.A. 2590.

We see no error in the Board's finding. "[A] court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR*, 550 U.S. at 418. Having already found the 40mg GA 3x/week limitation obvious, merely identifying the specific days for the thrice-weekly regimen is the natural application of the method, with a finite number of identified and predictable solutions, and requires not innovation but ordinary skill and common sense. *See id.* at 421.

CONCLUSION

In light of the foregoing, we conclude that the Board did not err in finding all claims of the Copaxone patents unpatentable as obvious.

AFFIRMED

COSTS

No costs.