UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ARGENTUM PHARMACEUTICALS LLC,
MYLAN PHARMACEUTICALS INC.,
BRECKENRIDGE PHARMACEUTICAL, INC., AND
ALEMBIC PHARMACEUTICALS, LTD.
Petitioners

v.

RESEARCH CORPORATION TECHNOLOGIES, INC.
Patent Owner

Case No. IPR2016-00204[1]
Patent No. RE38,551

PETITIONER BRECKENRIDGE PHARMACEUTICAL, INC.'S NOTICE OF APPEAL

[1] Case IPR2016-01101, Case IPR2016-01242, and Case IPR2016-01245 have been joined with this proceeding.

Pursuant to 37 C.F.R. § 90.2(a) and 35 U.S.C. §§ 141(c), 142, and 319, Breckenridge Pharmaceutical, Inc. ("Petitioner") respectfully gives notice that it appeals to the United States Court of Appeals for the Federal Circuit from the Patent Trial and Appeal Board's Final Written Decision entered on March 22, 2017 (Paper 85), and from all other underlying orders, decisions, rulings, and opinions.

For the limited purpose of providing the Director of the United States Patent and Trademark Office with the information specified in 37 C.F.R. § 90.2(a)(3)(ii), the issues on appeal include the Board's determination that Petitioners did not establish that claims 1-13 of U.S. Patent No. RE38,551 are unpatentable under 35 U.S.C. § 103 in view of the grounds of unpatentability on which trial was instituted (Paper 19) or which were asserted in the petition. The issues on appeal also include any finding or determination supporting or related to these issues, as well as all other issues decided adversely to Petitioners in any order, decision, ruling, or opinion.

Simultaneous with this filing and in accordance with 37 C.F.R. § 90.2(a)(1), this Notice of Appeal is being filed with the Director and served on Patent Owner in accordance with 37 C.F.R. § 42.6(e). This Notice of Appeal, along with the required fees, is also being filed with the Clerk's Office for the United States Court of Appeals for the Federal Circuit in accordance with Fed. Cir. R. 15(a)(1).

Respectfully Submitted,

Dated: May 24, 2017

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CERTIFICATES OF FILING AND SERVICE

I hereby certify that the foregoing Notice of Appeal was filed by hand delivery on this 24th day of May, 2017, with the Director of the United States Patent and Trademark Office, at the following address:

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I hereby certify that a true and correct copy of the foregoing Notice of Appeal was filed electronically by CM/ECF on this 24th day of May, 2017, with the Clerk's Office of the United States Court of Appeals for the Federal Circuit.

Pursuant to 37 C.F.R. § 42.6(e), I certify that I caused to be served a true and correct copy of the foregoing Notice of Appeal on the Patent Owner at the correspondence address of the Patent Owner as follows:

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Paper No. 85
Date Entered: March 22, 2017

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ARGENTUM PHARMACEUTICALS LLC,
MYLAN PHARMACEUTICALS INC.,
BRECKENRIDGE PHARMACEUTICAL, INC., and
ALEMBIC PHARMACEUTICALS, LTD.,
Petitioner,

v.

RESEARCH CORPORATION TECHNOLOGIES, INC.,
Patent Owner.

Case IPR2016-00204[1]
Patent RE38,551 E

Before JACQUELINE WRIGHT BONILLA, *Vice Chief Administrative Patent Judge*, FRANCISCO C. PRATS, and CHRISTOPHER G. PAULRAJ, *Administrative Patent Judges.*

PRATS, *Administrative Patent Judge*.

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

[1] Case IPR2016-01101, Case IPR2016-01242, and Case IPR2016-01245 have been joined with this proceeding.

I. INTRODUCTION

A. Statement of the Case

Argentum Pharmaceuticals LLC ("Argentum") filed a Petition requesting an *inter partes* review of claims 1–13 of U.S. Patent No. RE38,551 E (Ex. 1001, "the '551 patent"). Paper 2 ("Pet."). Research Corporation Technologies, Inc. ("Patent Owner") filed a Preliminary Response. Paper 9 ("Prelim. Resp.").

Upon review of those papers and cited information, we instituted trial as to claims 1–13 of the '551 patent in relation to the following two grounds of unpatentability (Paper 19, 23–24 ("Decision to Institute," or "Dec.")):

(1) Obviousness under 35 U.S.C. § 103(a) as to claims 1–9 over Kohn 1991[2] and Silverman[3]; and

(2) Obviousness under 35 U.S.C. § 103(a) as to claims 10–13 over Kohn 1991, Silverman, and the '729 patent.[4]

After the Decision to Institute, Mylan Pharmaceuticals, Inc. ("Mylan"), Breckenridge Pharmaceutical, Inc. ("Breckenridge"), and Alembic Pharmaceuticals, Ltd. ("Alembic"), were each joined as petitioners to the instant proceeding. *See* Case IPR2016-01101, Paper 12; Case IPR2016-01242, Paper 11; Case IPR2016-01245, Paper 12. Therefore, in

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[2] Kohn et al., *Preparation and Anticonvulsant Activity of a Series of Functionalized α-Heteroatom-Substituted Amino Acids*, 34 J. Med. Chem. 2444–52 (1991) ("Kohn 1991") (Ex. 1012).

[3] Richard B. Silverman, *The Organic Chemistry of Drug Design and Drug Action*, Academic Press (1992) ("Silverman") (Ex. 1013).

[4] Kohn et al., U.S. Patent No. 5,378,729, issued on Jan. 3, 1995 ("the '729 patent") (Ex. 1009).

the instant *inter partes* review, Argentum, Mylan, Breckenridge, and Alembic are, collectively, the "Petitioner."

Patent Owner filed a Response to the Petition (Paper 35; "PO Resp."), and Petitioner filed a Reply to the Patent Owner Response (Paper 52, "Pet. Reply").

Patent Owner filed a paper styled as "Patent Owner's Identification of Petitioners' Arguments and Evidence Outside the Scope of a Proper Reply and Improper Techniques that Circumvent Word Count." Paper 57.[5] Petitioner filed a response to that paper. Paper 63.

Both parties filed Motions to Exclude Evidence. Paper 72 ("Pet. Mot. to Exclude") and Paper 71 ("PO Mot. to Exclude").

Each party filed an Opposition to the other party's Motion to Exclude Evidence. Paper 78 ("Pet. Opp."); Paper 73 ("PO Opp."). Each party filed also a Reply to the other party's Opposition to the Motion to Exclude Evidence. Paper 81 ("Pet. Reply Opp."); Paper 80 ("PO Reply Opp.").

Patent Owner filed a Motion for Observations Regarding Cross-Examination as to each of Petitioner's three reply witnesses. Papers 65, 68, and 69. Petitioner filed responses to each of those motions. Papers 75–77.

An oral hearing was held on January 24, 2017, and the hearing transcript has been entered in the record. Paper 84 ("Tr.").[6]

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[5] The panel authorized this submission, and its response, by email. Ex. 2191.

[6] Patent Owner filed Objections to Petitioner's Demonstratives. Paper 82. In this Decision, we rely only on the arguments presented properly in the parties' briefs and the evidence of record. Our decision does not rely on any information presented solely in Petitioner's demonstrative exhibits. We, therefore, overrule Patent Owner's objections.

We have jurisdiction under 35 U.S.C. § 6(b). This Final Written Decision is entered pursuant to 35 U.S.C. § 318(a).

"In an inter partes review instituted under this chapter, the petitioner shall have the burden of proving a proposition of unpatentability by a preponderance of the evidence." 35 U.S.C. § 316(e).

Based on the record developed in this proceeding, we conclude that Petitioner has not established by a preponderance of the evidence that claims 1–9 of the '551 patent are unpatentable for obviousness over Kohn 1991 and Silverman, nor has Petitioner established by a preponderance of the evidence that claims 10–13 of the '551 patent are unpatentable for obviousness over Kohn 1991, Silverman, and the '729 patent.

Petitioner's Motion to Exclude Evidence is *denied-in-part* and *dismissed-in-part* as moot. Patent Owner's Motion to Exclude Evidence is *denied-in-part* and *dismissed-in-part* as moot.

B. Related Proceedings

Patent Owner identifies multiple lawsuits it has filed against different defendants in relation to the '551 patent in several U.S. district courts. Paper 6, 2–3. Most of those cases have been consolidated with *UCB, Inc. v. Accord Healthcare Inc.*, 1:13-cv-01206 (D. Del.). *Id.*; Pet. 1.

The parties also identify as related IPR2014-01126, where a panel previously denied an *inter partes* review based on a petition filed by a different petitioner, challenging the same claims of the same patent at issue here. *Actavis, Inc., v. Research Corporation Technologies, Inc.*, Case No. IPR2014-01126, Paper 22 (PTAB Jan. 9, 2015). Pet. 1; Prelim. Resp. 2; PO Resp. 18, n.6.

II. PRELIMINARY MATTER—SCOPE OF PETITIONER'S REPLY

We address initially the parties' contentions concerning the scope of Petitioner's Reply. As noted above, we authorized by email separate briefing on this issue. Ex. 2191.

As provided in 37 C.F.R. § 42.23(b), a "reply may only respond to arguments raised in the corresponding opposition or patent owner response." Thus, "a reply that raises a new issue or belatedly presents evidence will not be considered and may be returned. The Board will not attempt to sort proper from improper portions of the reply." Office Patent Trial Practice Guide, 77 Fed. Reg. 48,756, 48,767 (Aug. 14, 2012).

One indication that a new issue has been raised in a reply is where a petitioner submits "new evidence necessary to make out a *prima facie* case" of unpatentability of an original claim. *Id.; see also Intelligent Bio-Systems, Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1369–70 (Fed. Cir. 2016) (Board did not err or abuse its discretion in declining to consider new contentions and evidence in reply advanced to supplement unpatentability rationale presented in petition).

A. Arguments and Evidence Relating to the LeGall Thesis (Ex. 1008)

Having reviewed the parties' contentions (Paper 57, 1; Paper 63, 1), and the arguments at issue (Pet. Reply 28–29), we conclude that Petitioner's Reply exceeds the proper scope of a reply in relying on the LeGall Thesis, even as rebuttal. As Patent Owner notes, we concluded in our Decision to Institute that Petitioner failed to show that the LeGall Thesis constitutes prior art to the claims of the '551 patent and, therefore, declined to institute trial as to grounds relying on the LeGall Thesis. Dec. 8–12.

In its Reply, Petitioner seeks to advance additional evidence to supplement its original contention that the LeGall Thesis constitutes prior art. *See* Pet. Reply 28–29. Because Petitioner, thus, effectively seeks in its Reply to advance additional evidence to supplement its original contentions of unpatentability based on the LeGall Thesis, we agree with Patent Owner that Petitioner's Reply exceeds the proper scope of a reply. *See* Office Patent Trial Practice Guide, 77 Fed. Reg. at 48,767; *Intelligent Bio-Systems*, 821 F.3d at 1369–70.

Accordingly, our decision herein does not consider or rely on the arguments on pages 27–29 of the Reply regarding the LeGall Thesis, or the evidence advanced in support of those arguments. We note also that, although Petitioner contends that its supplemental evidence regarding the prior art status of the LeGall thesis was unavailable until June 23, 2016 (Pet. Reply 28), Petitioner does not advance persuasive evidence or argument supporting that contention.

B. The '301 Patent (Ex. 1019) as Support for Rationale to Select Compound 3l as Lead Compound

Having reviewed the parties' contentions (Paper 57, 1–2; Paper 63, 1), we conclude that the citations to the '301 patent[7] in the Reply do not exceed the proper scope of a reply. The'301 patent is relied upon in the same manner as relied upon in the Petition in relation to the grounds for which trial was instituted (*see*, *e.g.*, Pet. 46–47), and as rebuttal to Patent Owner's arguments about the state of the art.

[7] Kohn et al., U.S. Patent No. 5,654,301, issued on Aug. 5, 1997 ("the '301 patent") (Ex. 1019).

C. Unmet Need Arguments Based on Levetiracetam (Keppra®)

Having reviewed the parties' contentions (Paper 57, 2; Paper 63, 2), we conclude that the arguments based on levetiracetam/Keppra in the Reply do not exceed the proper scope of a reply, as they are proper rebuttal to Patent Owner's arguments regarding long-felt but unmet need.

D. Techniques Allegedly Circumventing Word Count

Patent Owner contends that Petitioner's Reply circumvents the word count limit set forth in 37 C.F.R. § 42.24(c)(1) by 195 words, through the use of 4 images and the omission of a space between "Ex." and the exhibit number when citing to exhibits. Paper 57, 2. Patent Owner contends that 140 of the 195 excess words may be accorded to the exhibit citation format used in the Reply. *Id.*

Petitioner responds that Patent Owner cites to no Board rule in its contentions regarding the exhibit citation format used in the Reply, and contends also that the exhibit citation format in the Reply conforms with the Federal Circuit rule for citing to appendices. Paper 63, 2. Petitioner contends further that Patent Owner's Response includes over 100 instances in which a space was omitted between "¶" and the paragraph number cited. *Id.* As to the use of images, Petitioner contends that "the images do not add text to the brief but merely act as citations to portions of exhibits in the record." *Id.*

When certifying word count, a party need not go beyond the routine word count supplied by their word processing program. Parties should be careful, however, not to abuse the process. Excessive words in figures, drawings or images, deleting spacing between words, or using excessive acronyms or abbreviations for word phrases, in order to circumvent the rules

on word count, may lead to expungement of a party's brief. *See Google, Inc., v. Ji-Lee*, Case No. IPR2016-00022, Paper 25 (PTAB Nov. 23, 2016).

In the present case, the alleged discrepancies in word count in Petitioner's Reply are noted. Based on the record presented, we exercise our discretion to not decline to limit our consideration of the Reply on this basis.

III. PATENTABILITY

A. The '551 Patent (Ex. 1001)

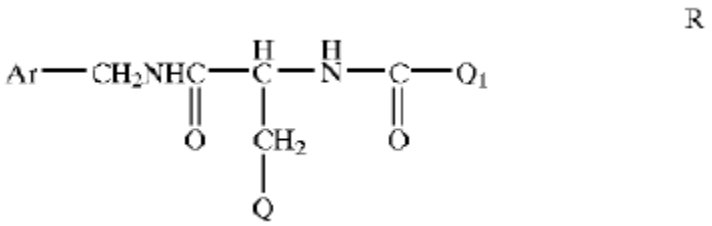
The '551 patent relates to "enantiomeric compounds and pharmaceutical compositions useful in the treatment of epilepsy and other CNS [central nervous system] disorders." Ex. 1001, 1:21–23. The '551 patent discloses that, although many anticonvulsant drugs were well known at the time of the invention, a significant number of those drugs exhibited liver toxicity when administered chronically. *Id.* at 1:45–3:6.

Seeking to address the shortcomings of prior art anticonvulsant agents, the '551 patent discloses "a group of compounds that is generally potent, exhibit minimal neurological toxicity, has a high protective index and is relatively non-toxic to the body organs, including the liver upon multiple dosing." *Id.* at 3:56–60. The disclosed compounds are derivatives of the amino acid serine. *See id.* at 5:20–8:61 (describing synthetic schemes using D-serine as a starting material).

One of those serine derivatives is (R)-N-benzyl-2-acetamide-3-methoxypropionamide, also referred to in the '551 patent as "BAMP." *Id.* at 11:21–13:14 (Examples 1 and 2), 24:56–58.

(R)-N-benzyl-2-acetamide-3-methoxypropionamide is also known as "lacosamide." *See* Pet. 6; PO Resp. 6.

Claim 1 of the ’551 patent, the sole independent claim under review, reads as follows:

> 1. A compound in the R configuration having the formula:
>
> 
>
>
> wherein Ar is phenyl which is unsubstituted or substituted with at least one halo group;
> Q is lower alkoxy, and
> Q_1 is methyl.

Id. at 38:8–23. Claims 2–9 are compound claims that depend directly or indirectly from claim 1. *Id.* at 38:24–40.

Claim 8 of the ’551 patent is specifically directed to lacosamide, and recites “[t]he compound according to claim 1 which is (R)-N-benzyl 2-acetamide-3-methoxypropionamide.” *Id.* at 38:37–38.

Claim 10 of the ’551 patent recites “[a] therapeutic composition comprising an anticonvulsant effective amount of a compound according to any one of claims 1–9 and a pharmaceutical carrier therefor.” *Id.* at 38:41–43.

Claims 11–13 are directed to therapeutic methods. *Id.* at 38:44–51. Claim 11 recites “[a] method of treating central nervous system disorders in an animal comprising administering to said animal in need thereof an anticonvulsant effective amount of a compound according to any one of claims 1–9.” *Id.* at 38:44–47.

Claim 12 recites "[t]he method according to claim 11 wherein the animal is a mammal," and claim 13 recites "[t]he method according to claim 12 wherein the mammal is a human." *Id.* at 38:48–51.

B. Claim Construction

In an *inter partes* review, claim terms in an unexpired patent are given their broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2142 (2016) (affirming applicability of broadest reasonable construction standard to *inter partes* review proceedings). Under that standard, claim terms are generally given their ordinary and customary meaning, as understood by one of ordinary skill in the art in the context of the entire disclosure. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007).

In our Decision to Institute, based on the parties' initial submissions, we set out preliminary constructions for the terms "compound in the R configuration" in claim 1, and "therapeutic composition" in claim 10. Dec. 5–8. As evidenced by the discussion below, however, the construction of neither of those terms, nor any other claim term, is critical to our final disposition of the issues developed during trial. Accordingly, we conclude that, for the purposes of this decision, no claim term requires express construction. *See Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999) (only those claim terms in controversy need to be construed, and only to the extent necessary to resolve the controversy).

C. Obviousness—Claims 1–9

Petitioner contends that the compounds recited in claims 1–9 would have been obvious over Kohn 1991 and Silverman, and relies on a

declaration by Dr. Binghe Wang (Ex. 1002 ("Wang Decl.")), in support of that contention. Pet. 44–48.

Patent Owner contends to the contrary, and in support of its contentions relies on declarations by William R. Roush, Ph.D. (Ex. 2036 ("Roush Decl.")), Carl W. Bazil, M.D., Ph.D. (Ex. 2038 ("Bazil Decl.")), and Christopher A. Vellturo, Ph.D. (Ex. 2132 ("Vellturo Decl.)). PO Resp. 1–45, 51–61.

In its Reply to Patent Owner's Response, Petitioner relies on a second declaration by Dr. Binghe Wang (Ex. 1084 ("Wang Reply Decl.")), as well as declarations by DeForest McDuff, Ph.D. (Ex. 1086 ("McDuff Decl.")), and Kathryn A. Davis M.D., MSTR (Ex. 1087 ("Davis Decl.")). Pet. Reply 1–14, 16–28.

As the Supreme Court has stated, when evaluating claims for obviousness, "the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007) (quoting *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966)). Secondary considerations, if present, also must be considered. *Id.*

1. Level of Ordinary Skill in the Art

Petitioner contends that the relevant art is medicinal chemistry. Pet 12. As to the level of ordinary skill in that art as of March 15, 1996 (the earliest possible priority date of the '551 patent), Petitioner contends as follows:

> [A] POSA [person of ordinary skill in the art] would have a Ph.D. in organic or medicinal chemistry and at least a few years of experience in medicinal chemistry, including in the development

> of potential drug candidates. Ex. 1002, ¶ 13 [Wang Decl.]. The POSA would also include a person having a Bachelor's or Master's degree (organic chemistry or medicinal chemistry) if such a person had more years of experience in medicinal chemistry and the development of potential drug candidates. *Id.* With experience in drug development, the POSA would have an appreciation of the diseases and ailments a particular drug candidate is intended to treat, but would not necessarily be a medical doctor or clinician. The POSA would know how to evaluate the physical and biological properties of chemical compounds and would be able to conduct, or otherwise have access to resources that could conduct, *in vitro* and *in vivo* evaluations of biological and toxicity properties of chemical compounds. *Id.*

Pet. 12. Patent Owner does not controvert Petitioner's characterization of the relevant art, or the level of ordinary skill in that art, nor does Patent Owner advance a specific assertion of its own as to the level of ordinary skill. *See, generally*, PO Resp.

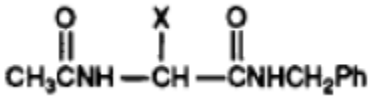
Accordingly, when evaluating the parties' contentions regarding the scope and content of the prior art, and the differences between the prior art and the challenged claims, we take into consideration Petitioner's assertions regarding the level of ordinary skill. We also consider that the cited references provide evidence as to the level of ordinary skill in the art. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001).

2. Kohn 1991 (Ex. 1012)

Kohn 1991, a publication coauthored by Harold Kohn, the sole inventor of the '551 patent, discloses that previous prior art studies had "reported the excellent anticonvulsant activity of certain functionalized amino acid derivatives [FAAs]." Ex. 1012, 2444. In the study disclosed in Kohn 1991, the authors present the "synthesis and anticonvulsant properties

of a novel series of α-heteroatom-substituted amino acid derivatives (26 examples)." *Id.*

Kohn 1991 sets out the following general formula for the FAAs it tested (*id.* at 2445 (Table 1)):



Kohn 1991 explains that the moiety at the "X" position is termed "the α-substituent." *Id.* at 2444.

Table 1 of Kohn 1991 lists the moiety substituted at the "X" position for each of the 26 compounds studied, numbered "**3a**" through "**3z**." *Id.* at 2445. The compounds were evaluated for anticonvulsant activity in mice using the maximal electroshock seizure test (MES), and a median effective dose (ED_{50}) for that test was determined for each compound. *Id.* at 2444–45. As in our Decision to Institute, we note that the lower the MES ED_{50}, the more potent the compound. *See* Dec. 13, n.8.

Table 1 also discloses the MES ED_{50} for several compounds previously tested and synthesized by the same group of investigators (compounds 2a through 2d), as well as several known antiepileptic drugs (AEDs), including phenytoin, phenobarbital, and valproate. Ex. 1012, 2445.

Kohn 1991 discloses that the "most active compounds were (*R,S*)-2-acetamido-*N*-benzyl-2-(methoxyamino)acetamide (**3l**) and (*R,S*)-2-acetamido-*N*-benzyl-2-(methoxymethylamino)acetamide (**3n**). After ip [intraperitoneal] administration, the MES ED values for **3l** (6.2 mg/kg) and **3n** (6.7 mg/kg) compared favorably with phenytoin (9.50 mg/kg)." Ex. 1012, 2444 (abstract).

Kohn 1991 concludes:

> The pharmacological data obtained in this investigation provided additional information concerning the structure activity profile of functionalized amino acid anticonvulsants. The biological activities for **3** reinforced our notions that stringent steric and electronic requirements exist for maximal anticonvulsant activity in this class of compounds. The potencies of **3l** and **3n** in the MES test were comparable to those of phenytoin and **2d**. Additional studies in progress are aimed at investigating the generality of this class of compounds, as well as their mode of action.

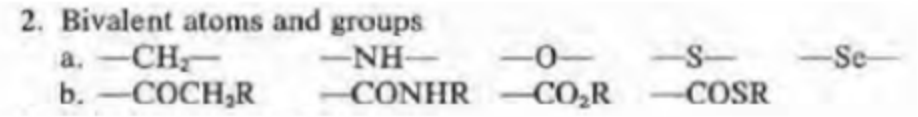
Id. at 2447.

3. Silverman (Ex. 1013)

Silverman presents a chapter entitled "Drug Discovery, Design, and Development" in a book entitled "The Organic Chemistry of Drug Design and Drug Action." Ex. 1013, title page; *see also id.* at 4. In a section discussing "Bioisosterism," Silverman teaches that:

> *Bioisosteres* are substituents or groups that have chemical or physical similarities and which produce broadly similar biological properties. Bioisosterism is a lead modification approach that has been shown to be useful to attenuate toxicity or to modify the activity of a lead, and it may have a significant role in the alteration of metabolism of a lead. There are classical isosteres and nonclassical isosteres.

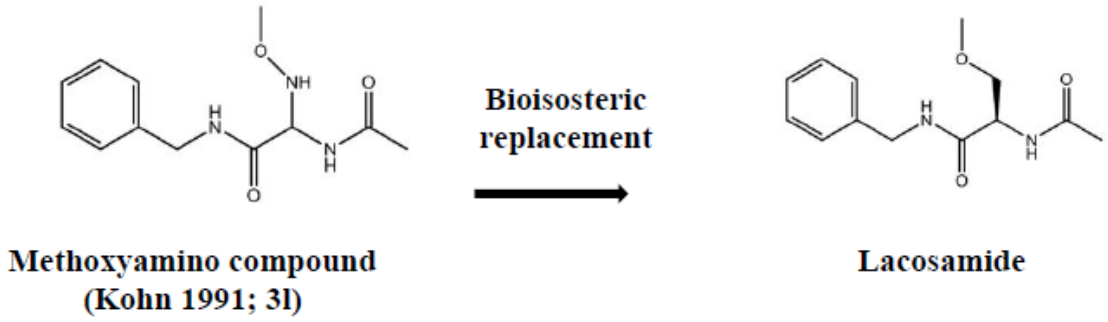
Id. at 19 (citations omitted). Table 2.2 on the same page of Silverman presents "Classical Isosteres," including:



Id.

4. Analysis—Lead Compound Inquiry

Petitioner presents a summary of its initial obviousness contentions in the following diagram:



Pet. 44.

Petitioner contends that an ordinary artisan would have selected compound 3l from Kohn 1991 as a lead compound, based on its potency. *Id.* As seen in its diagram, Petitioner contends that, having selected compound 3l as a lead, the ordinary artisan then would have used the technique of bioisosterism taught in Silverman and replaced the -NH- group of the methoxyamino substituent with a -CH_2- group, thereby yielding the methoxymethyl substituent seen in the lacosamide molecule, and producing a racemic mixture of lacosamide. *Id.* at 45.

Petitioner contends that, from the resulting racemic mixture of lacosamide, an ordinary artisan would have had good reason, based at least on Kohn 1991 itself, to isolate the R-isomer of lacosamide. *Id.* at 47. Although Petitioner does not state so expressly, based on the above contentions, we understand Petitioner as contending that each of claims 1–9 encompasses R-lacosamide.[8]

[8] Patent Owner infers that claim 6 does not cover lacosamide. *See* PO Resp. 23, n.9 (contending Petitioner's showing is insufficient as to claim 6); *see*

As explained by our reviewing court, "[t]o establish obviousness in cases involving new chemical compounds, [the proponent of the compounds' obviousness] must identify some reason that would have led a chemist to modify a known compound." *Bristol-Myers Squibb Co. v. Teva Pharmaceuticals USA, Inc.*, 752 F.3d 967, 973 (Fed. Cir. 2014).

"Generally, an obviousness inquiry concerning such 'known compounds' focuses on the identity of a 'lead compound.'" *Id.* (quoting *Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008)). "A lead compound is a compound in the prior art that would be 'a natural choice for further development efforts.'" *Id.* (quoting *Altana Pharma AG v. Teva Pharms. USA, Inc.*, 566 F.3d 999, 1008 (Fed. Cir. 2009). "The motivation to modify that lead compound can come from any number of sources and need not necessarily be explicit in the art." *Id.*

Consistent with the flexible principles of obviousness enunciated in *KSR v. Teleflex*, to demonstrate that a claimed compound would have been obvious, "a showing that the prior art would have suggested making *the specific molecular modifications* necessary to achieve the claimed invention [i]s also required." *Takeda Chemical Industries, Ltd. v. Alphapharm Pty.*,

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also id. at 51, n.15 (not including claim 6 among claims asserted as covering lacosamide). We conclude, however, that claim 6 covers lacosamide.

Claim 1, from which claim 6 depends, recites as to the relevant moiety that "Ar is phenyl which is unsubstituted or substituted with at least one halo group." Ex. 1001, 38:19–20. Claim 6 recites, in its entirety, "[t]he compound according to claim 1 wherein halo is fluoro." *Id.* at 38:32–33. Thus, claim 6 does not limit the "Ar" moiety of claim 1 to a substituted moiety, and, therefore, encompasses a compound having the unsubstituted phenyl group of lacosamide.

Ltd., 492 F.3d 1350, 1357 (Fed. Cir. 2007) (internal quotations omitted, emphasis added).

In the present case, even assuming *arguendo* that an ordinary artisan would have selected compound 3l of Kohn 1991 as a lead compound for further development, Petitioner does not persuade us that the prior art of record would have suggested making the specific modification to compound 3l required to yield lacosamide.

Petitioner identifies two reasons for modifying the methoxyamino moiety of compound 3l: "First, the methoxyamino moiety is not a common moiety used in the compounds the result in commercial pharmaceuticals. Ex. 1002, ¶ 106 [Wang Decl.]. Second, the methoxyamino moiety may present synthetic and stability issues." Pet. 45 (citing Ex. 1002 ¶ 106).

As to the specific modification to the methoxyamino group of compound 3l required to arrive at lacosamide, Petitioner contends that bioisosteric replacement of the -NH- group of compound 3l's methoxyamino substituent with a -CH2- group converts the methoxyamino substituent into a methoxymethyl group, which "is a more common and acceptable moiety for pharmaceutically active compounds." *Id.* (citing Ex. 1002 ¶ 107).

Petitioner contends that data from Kohn 1991 confirms the expected bioisosteric equivalence of the methoxyamino substituent of compound 3l with the methoxymethyl substituent of lacosamide. Pet. 45–46. To that end, Petitioner points out that the activity of compound 3l (R = $-NHOCH_3$) has about a ten-fold higher activity than its methoxy-lacking amine-containing counterpart compound (R = $-NH_2$), and contends that this disclosure would have suggested to an ordinary artisan that substituting a methoxymethyl group at the same position to yield lacosamide (R = $-CH_2OCH_3$) would have

been expected to achieve a similar 10-fold increase over the activity of the methoxy-lacking methyl-containing counterpart compound (R = -CH_3). *Id.* at 46.

In response, Patent Owner advances a number of reasons why the prior art would not have suggested converting the methoxyamino group of compound 3l to the methoxymethyl group of lacosamide. PO Resp. 23–45.

Having considered the rationale and supporting evidence advanced by Petitioner alongside Patent Owner's arguments and supporting evidence, Patent Owner persuades us that Petitioner has not shown sufficiently that the prior art of record would have suggested making the specific modification to compound 3l required to yield lacosamide.

Petitioner relies on the uncorroborated testimony of its expert, Dr. Wang, as support for its contention that compound 3l's methoxyamino group is an uncommon moiety among commercial pharmaceuticals that presents potential synthetic and stability issues, and also for its contention that the posited substitute, a methoxymethyl group, is a more common and acceptable moiety for pharmaceutically active compounds. *See* Pet. 44–45; *see also* Ex. 1002 ¶¶ 106, 107 (Wang Decl.) (citing no documentary support).

As stated in 37 C.F.R. § 42.65(a), "[e]xpert testimony that does not disclose the underlying facts or data on which the opinion is based is entitled to little or no weight." We, nonetheless, acknowledge Dr. Wang's education and experience (Ex. 1002 ¶¶ 6–10, Appendix A), and note that Patent Owner does not dispute specifically the accuracy of Dr. Wang's assertions in this regard. We thus acknowledge that, as a general principle in the art of medicinal chemistry, an ordinary artisan seeking to develop a commercial

pharmaceutical compound ordinarily would have considered the substitution of a methoxyamino group with another more common and acceptable moiety, particularly because of any potential synthetic and stability issues associated with the methoxyamino group in the compound. Petitioner, however, does not identify a specific reason as to why that substitution would have been considered desirable for any of the prior art anticonvulsant compounds taught by Kohn 1991, let alone compound 3l identified as the lead compound.

In contrast to the general suggestion in the art, Patent Owner advances evidence that, *as to the specific group of compounds described in Kohn 1991*, conversion of compound 3l's methoxyamino group to a different group, including the posited methoxymethyl group, would have been viewed as undesirable. In particular, as Patent Owner contends (PO Resp. 24–29), compounds in Kohn 1991 and related publications lacking a methoxyamino or nitrogen-containing moiety at the α-substituent, or "X" position of the molecule, have a reduced activity as compared to compounds having the methoxyamino or nitrogen-containing substituent.

For example, as Patent Owner contends, replacing the amine group at position X of Kohn 1991's compound 3a (ED_{50} = 65.1 mg/kg) with a methyl group, yielding compound 2a (ED_{50} = 76.5 mg/kg), results in a decrease in activity. *See* Ex. 1012, 2445 (Table 1 of Kohn 1991).

A similar decrease in activity is seen when comparing Kohn 1991's nitrogen-containing compound 3o (ED_{50} = 31.4 mg/kg (*see id.*)) to its

carbon-containing counterpart described in Kohn 1993,[9] compound 21 a/b (ED_{50} = 51.7/89.8 mg/kg, respectively (*see* Ex. 1017, 3351 (Table 1)).

Similar decreases in activity are seen when replacing a nitrogen-containing moiety at position X of Kohn 1991's compounds 3a, 3b, and 3c (ED_{50} = 65.1, 44.5, and 42.4 mg/kg, respectively) with a corresponding oxygen-containing moiety in compounds 3r, 3s, and 3t (ED_{50} = 80.1, 98.3, and 62.0 mg/kg, respectively). *See* Ex. 1012, 2445.

The reduction in activity seen in Kohn 1991 when replacing a nitrogen-containing moiety at position X with a non-nitrogen-containing moiety is consistent with a teaching, identified by Patent Owner (PO Resp. 27), in a later prior art publication co-authored by Dr. Kohn, i.e., Kohn 1994 (Ex. 2055).[10] As stated in Kohn 1994, when testing related compounds having the same base molecular structure, the investigators found that "excellent protection against MES-induced seizures by [functionalized α,α-diamino acids] can be achieved by incorporation of a *basic* C(α)-amino substituent." *Id*. at 691.

Both parties' experts agree that an ordinary artisan would have understood Kohn 1994's reference to a basic C(α)-amino substituent as

[9] Harold Kohn et al., *Synthesis and Anticonvulsant Activities of α-Heterocyclic α -Acetamido-N-benzylacetamide Derivatives*, 36 J. Med. Chem. 3350–3360 (1993) (Ex. 1017) ("Kohn 1993").

[10] Harold Kohn et al., *Anticonvulsant Properties of N-Substituted a,a-Diamino Acid. Derivatives*, 83 J. Pharm. Sci. 689–691 (1994) (Ex. 2055) ("Kohn 1994").

encompassing a methoxyamino group. *See* Ex. 2036 ¶ 252 (Roush Decl.)[11] ("[A] POSA would examine the data and conclude that activity was best when the compound contained a nitrogen atom capable of accepting a hydrogen bond or serving as a ligand in the biological receptor binding site."); *see also* Ex. 2194, 194 (Second Wang Deposition).[12]

The first sentence in the conclusion section of Kohn 1994 also supports Patent Owner's contention that an ordinary artisan would not have been motivated to change the methoxyamino group of compound 3l of Kohn 1991 to a different chemical moiety. That sentence states:

> The composite data indicated that most structural modifications at the α-amino site in functionalized α,α-diamino acids led to a decrease in the anticonvulsant activity after intraperitoneal administration to mice when compared to the simple *N*-ethylamino adduct **2a** [of Kohn 1991], while none of the compounds approached the superior activity observed for the *N*-hydroxylamino derivatives **2c** and **2d** [of Kohn 1991].

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[11] In view of Dr. Roush's education and experience (*see* Ex. 2036 ¶¶ 4–26 (Roush Decl.)), we credit his opinion on the matters for which Patent Owner advances his testimony.

[12] Deposition of Dr. Binge Wang, Ph.D., December 10, 2016 (Ex. 2194) ("Second Wang Deposition"). In citing to the Second Wang Deposition, we cite to page numbers appearing at the top right portion of each page. As stated in therein (emphasis added):

> Q. But Dr. Kohn considered the methoxyamino group to be a basic amino substituent, correct?
>
> . . .
>
> THE WITNESS: So he had a compound that's -- let's see. He has di-amino compound and then he also has -- let me see. *Yeah, he also has methoxyamino*, ethylamino and -- yeah, he has a range of substitutes in there, and among them, he also had hydroxy amino.

Ex. 2194, 194.

Ex. 2055, 691 (endnote citations to Kohn 1991 inserted in brackets). Dr. Wang explains in his Reply Declaration that compound 2c, referred to in the above passage as having "superior activity," "is the same as Compound 3l from Kohn 1991." Ex. 1084 ¶ 241.

In addition, Patent Owner advances evidence that an ordinary artisan also would have understood that replacing the methoxyamino group of compound 3l of Kohn 1991 with a methoxymethyl group would have resulted in a molecule with a significantly different overall conformation, and, therefore, a significantly different interaction with receptors modulating anticonvulsant activity and neurotoxicity, as well as a different biological activity. PO Resp. 36–39 (citing Ex. 2036 ¶¶ 288, 294–295 (Roush Decl.); also citing Ex. 2012 (Heathcock Trial Testimony).[13]

To that end, Dr. Roush testifies that, based on a software-generated comparison of the three-dimensional structures of compound 3l and racemic lacosamide, the overall conformations of the two molecules are "very different." Ex. 2036 ¶ 294. Dr. Roush testifies further:

> As of March 1996, it was not known how FAAs interacted with the receptors to led [sic, lead] to anticonvulsant activity or neurotoxicity. These computer generated diagrams, which a POSA could have conceived of and easily generated in March 1996, confirms that compounds with nitrogen based groups at the α-carbon would not have interacted with the receptors (that

[13] As Patent Owner explains, "Exhibit 2012 ["Heathcock Trial Testimony"] is the November 9, 2015 direct, cross, and redirect trial testimony of Dr. Heathcock (appearing on behalf of defendants, including the prior petitioners) in the consolidated Delaware litigation involving the '551 patent (*UCB, Inc., et al. v. Accord Healthcare, Inc., et al.*, No. 13-1206 (LPS) (D. Del.))." PO Resp. 18, n.6. In citing to the Heathcock Trial Testimony we cite to the page numbers at the top right portion of the page, as do the parties.

> modulate either anticonvulsant activity or neurotoxicity) in the same way as compounds with carbon-based groups at the α-carbon. Given how small changes at the α-carbon led to large changes in anticonvulsant activity and neurotoxicity, it seems unlikely that two compounds that occupy such different space would fit into the same binding pocket on the requisite receptor. Therefore, a POSA would not reasonably believe that such a modification would have resulted in a successful AED.

Id. ¶ 295.

The trial testimony of Dr. Heathcock, whom neither party disputes is an expert in the art at issue here, cited by Patent Owner and Dr. Roush (PO Resp. 39; Ex. 2036 ¶ 294), is consistent with Dr. Roush's testimony that an ordinary artisan would have expected a significantly different molecular conformation, and a concomitant change in biological properties, when substituting a carbon for a nitrogen in the α-substituent of the FAAs described in Kohn 1991:

> [THE WITNESS]. I might point out that these are molecules that are going to be shaped rather differently in three dimensions because the carbon has got four things attached to it and the nitrogen only has three. . . . That's why those two things are so different even though they have the same formula.
> Q. But that's true, any time you substitute a carbon for a nitrogen, a carbon has four bonds and a nitrogen has three?
> A. I was simply pointing out the case you showed me, one with 51 and one with 98 I think they were, although they looked like the same compound, they differ by a factor of about two in potency and that's because of that shape and there is only one possible compound when there is a nitrogen.

Ex. 2012, 190:22–191:13.

We agree with Patent Owner (PO Resp. 38) that, given Kohn 1991's teaching that "stringent steric and electronic requirements exist for maximal

anticonvulsant activity in this class of compounds" (Ex. 1012, 2447), the expected substantial change to the conformation of the overall molecule is significant evidence that an ordinary artisan would not have been motivated to replace the methoxyamino group of compound 3l, the most potent compound taught in Kohn 1991, with a methoxymethyl group.

In sum, we acknowledge Dr. Wang's testimony, discussed above, that due to a methoxyamino group's potential synthetic and stability issues, and uncommonness in commercial pharmaceuticals, an ordinary artisan may have had a reason to replace such a group with a more common and acceptable moiety, such as a methoxymethyl group, in chemical compounds generally. Nonetheless, as also discussed above, the evidence advanced by Patent Owner shows that, *as to the specific FAA compounds of Kohn 1991*, an ordinary artisan would have understood that compound 3l's methoxyamino moiety was considered a basic C(α)-amino substituent that conferred significant activity to the compound, and replacement of that moiety with other substituents would have led to a reduction in activity. As also discussed above, Kohn 1991 teaches that "stringent steric and electronic requirements exist for maximal anticonvulsant activity in this class of compounds" (Ex. 1012, 2447), whereas an ordinary artisan would have understood that substituting a methoxymethyl group for the methoxyamino group of Kohn 1991's compound 3l would result in a compound with a significantly different conformation and biological activity.

Thus, assessing Petitioner's evidence of a more general motivation for substituting a methoxymethyl group for the methoxyamino group of compound 3l, against Patent Owner's evidence specifically suggesting that an ordinary artisan would not have viewed the posited substitution as being

desirable, we find that the weight of the evidence significantly favors Patent Owner's position. Overall, the evidence before us indicates that an ordinary artisan lacked motivation, as well as a reasonable expectation of success, for making the specific substitution to Kohn 1991's compound 3l, required to arrive at lacosamide. That is, we agree with Patent Owner that Petitioner has not shown sufficiently that the prior art of record would have suggested making the specific modification to compound 3l required to yield lacosamide.

Petitioner's rebuttal arguments do not persuade us to the contrary. Petitioner reiterates its contention that an ordinary artisan, based on an methoxyamino group's potential stability issues and uncommonness, would have employed the "well-known $NH \rightarrow CH_2$ bioisosteric replacement." Pet. Reply 10 (citing Ex. 1002 ¶ 107 (Wang Decl.); Ex.1084 ¶¶ 31–37, 244–246 (Wang Reply Decl.)). Petitioner notes in particular the teaching in Silverman that "[b]iososterism is a lead modification approach that has been shown to be useful to attenuate toxicity, or to modify the activity of a lead." Pet. Reply 10 (citing Ex.1013, 14 (Silverman)).

Petitioner does not explain with any specificity, however, why an ordinary artisan would have modified the methoxyamino group of compound 3l in particular, given the evidence discussed above indicating the undesirability of making such a modification. That bioisosterism was a well-known technique for modifying lead compounds, and that the methoxyamino group of compound 3l may have had potential stability issues, does not explain sufficiently why an ordinary artisan would have ignored the prior art teachings identified by Patent Owner that, *in this specific instance*, the basic C(α)-amino substituent in the methoxyamino was

important to the potency of this class of compounds, and significant changes to the molecular conformation of the molecule were expected when that moiety was replaced with something else, and that an ordinary artisan, therefore, would have concluded that substitution at that moiety would have been undesirable.

We acknowledge Silverman's teaching, noted above, that bioisosterism has been shown to be useful to attenuate toxicity in lead compounds. As Patent Owner contends (PO Resp. 39–40), however, Petitioner does not advance specific evidence suggesting an ordinary artisan would have understood that modifying the methoxyamino group of Kohn 1991's compound 3l would have reduced that compound's toxicity. Indeed, rather than exhibiting a level of toxicity that might require attenuation, compound 3l, as Patent Owner contends, "was already among the better of the reported P.I. [protective index] values for FAAs as of 1996." PO Resp. 39 (citing Ex 2036 ¶ 296 (Roush Decl.)).[14] In advocating selection of compound 3l as a lead compound, Petitioner effectively concedes this point. *See* Pet. Reply 6 ("**Compound 3l Had High Potency, Good Neurotoxicity, and A 'Top Five' Protective Index**").

[14] Dr. Roush explains that the "protective index," or P.I., is a measure of a compound's neurotoxicity, "mathematically calculated by dividing the TD_{50} value [median toxic dose, *see, e.g.*, Ex. 1012, 2445 (Kohn 1991)] obtained from a neurotoxicity test by the compound's ED_{50} value obtained from an anticonvulsant activity test. Compounds with higher P.I.s were generally viewed as more promising candidates than compounds with lower P.I.s." Ex. 2036 ¶ 105 (Roush Decl.). *See also* Ex. 1001, 3:19 ("protective index . . . measures the relationship between the doses of a drug required to produce undesired and desired effects, and is measured as the ratio between the median toxic dose and the median effective dose (TD_{50}/ED_{50})").

Petitioner asserts that "Dr. Roush has limited experience with lead compound analysis and has instead focused on random drug screening." Pet. Reply 10 (citing Ex. 1050, 70–71 (Roush Deposition)).[15] As seen above, however, each of Patent Owner's contentions regarding the posited modification to compound 3l, as well as the supporting testimony of Dr. Roush, are based on prior art disclosures and information which an ordinary artisan would have been aware of before the earliest possible priority date for the claims 1–9 of the '551 patent, a fact Petitioner does not dispute. Thus, that Dr. Roush's specific research pursuits focused on high throughput analysis (*see* Ex. 1050, 70–71) does not persuade us that his testimony is unreliable, particularly given his education and considerable overall experience (*see* Ex. 2036 ¶¶ 4–26 (Roush Decl.)).

We acknowledge, as Petitioner contends (Pet. Reply 11), that claim 44 of the '301 patent recites a methoxymethyl group. Ex. 1019, 94:12–13 (the '301 patent). Other than the mere presence of that moiety in claim 44, however, Petitioner does not identify any specific evidence or teaching in the '301 patent controverting or undermining the evidence, discussed above, supporting Patent Owner's position that modifying compound 3l's methoxyamino group would have been viewed as undesirable. Thus, that claim 44 of the '301 patent recites a methoxymethyl group does not persuade us that an ordinary artisan would have been motivated to make

[15] Deposition of William R. Roush, October 21, 2016 (Ex. 1050) ("Roush Deposition"). In citing to the Roush Deposition, Petitioner appears to cite to the page numbers inserted at the bottom right portion of the pages. We do the same, for consistency.

Petitioner's posited substitution, given the evidence to the contrary, discussed above, advanced by Patent Owner.

We acknowledge, as Petitioner contends (Pet. Reply 11), that Kohn 1993 teaches that "improved activity resulted by the positioning of a heteroatom two atoms removed from the C(α)-site." Ex. 1017, 3354 (Kohn 1993). As noted above, however, in each of the examples cited by Patent Owner, when nitrogen at the α-carbon substituent was substituted with a non-nitrogen-containing substituent, potency was reduced. Indeed, Petitioner does not identify any specific example in the prior art of record in which substitution of a non-nitrogen-containing moiety for a nitrogen at the α-carbon substituent failed to reduce potency. As discussed above, moreover, these reductions in potency must also be viewed alongside the evidence advanced by Patent Owner regarding the prior art's recognition of the importance of the basic C(α)-amino substituent at the α-carbon to potency, as well as the expectation of significant conformational changes when converting the nitrogen-containing group to something else.

We acknowledge Petitioner's contention (Pet. Reply 11–12) that compound 3l was one of the most potent FAAs described in the prior art, with one of the best protective indices. Although such factors might provide a reason to select compound 3l as a lead compound, Petitioner does not explain sufficiently why those factors would have led an ordinary artisan to modify compound 3l in the specific manner required to yield lacosamide, particular given the evidence to the contrary, discussed above.

In sum, having considered the arguments and supporting evidence advanced by both parties, we find, for the reasons discussed, that the weight of the evidence significantly favors Patent Owner's position that an ordinary

artisan would have lacked motivation, as well as a reasonable expectation of success, for making the specific substitution to Kohn 1991's compound 3l required to arrive at lacosamide. We, therefore, find that Petitioner has not shown sufficiently that the prior art of record would have suggested making the specific modification to compound 3l required to yield lacosamide.

Thus, even if we had no evidence of objective evidence of nonobviousness before us, we would conclude that Petitioner has failed to meet its burden to establish by a preponderance of the evidence that challenged claims 1–9 would have been obvious. To completely address all arguments and evidence before us, we also weigh Patent Owner's asserted objective evidence of nonobviousness, as discussed below, when making our ultimate determination as to the obviousness of the compounds recited in claims 1–9.

5. Objective Indicia of Nonobviousness

When evaluating claims for obviousness, the objective indicia of nonobviousness must be considered, alongside the teachings in the prior art, "as part of all the evidence, not just when the decisionmaker remains in doubt after reviewing the art." *Eurand, Inc. v. Mylan Pharm. Inc. (In re Cyclobenzaprine Hydrochloride Extended–Release Capsule Patent Litig.)*, 676 F.3d 1063, 1076 (Fed. Cir. 2012) (quoting *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538–39 (Fed. Cir. 1983)).

"Indeed, evidence of secondary considerations may often be the most probative and cogent evidence in the record. It may often establish that an invention appearing to have been obvious in light of the prior art was not." *Id.* at 1075–76 (quoting *Stratoflex*, 713 F.2d at 1538). In *Eurand v. Mylan*, the court explained further that, "not only is *Stratoflex* the law, it is sound in

requiring that a fact finder consider the objective evidence before reaching an obviousness determination. The objective considerations, when considered with the balance of the obviousness evidence in the record, guard as a check against hindsight bias." *Id.* at 1079.

Objective evidence of nonobviousness may include solving a long-felt but unsolved need, failure of others, unexpected results, commercial success, copying, licensing, industry praise, and industry skepticism. *Graham v. Deere*, 383 U.S. at 17; *Transocean Offshore Deepwater Drilling, Inc. v. Maersk Drilling USA, Inc.*, 699 F.3d 1340, 1347, 1349–1355 (Fed. Cir. 2012).

As discussed in more detail below, we find that not all of Patent Owner's arguments and evidence of objective indicia are probative. That said, we find that Patent Owner offers significant evidence of satisfying a long felt, but unmet, need, as well as probative evidence of commercial success, which further supports our determination that Petitioner has not established by a preponderance of the evidence that the compounds of challenged claims 1–9 would have been obvious in view of Kohn 1991 and Silverman.

a. Unexpected Results

Patent Owner contends that "the objective indicia concerning lacosamide and its commercial embodiment Vimpat® confirm that the inventions of the '551 patent were not obvious in 1996." PO Resp. 51–52.

As to unexpected results specifically, Patent Owner contends:

> [A] POSA would have had no reason to expect that any FAA, let alone lacosamide, would possess the favorable combination of ideal properties for which Vimpat® has been widely praised: high potency, low neurotoxicity, high protective index, minimal liver

> toxicity, desirable dosing and formulations, favorable pharmacokinetic properties, minimal dose-dependent and reversible side effects, little to no drug-drug interaction, and a distinct and novel mechanism of action.

PO Resp. 52. In particular, Patent Owner contends, given the lack of prior art pharmacological data for lacosamide in particular and FAAs in general, and given the unknown nature of the mode of action of FAAs, contrasted with the clinical data for antiepileptic drugs generally showing a variety of shortcomings, including "serious and sometimes irreversible adverse effects, drug-drug interactions, complicated pharmacokinetics, and limited formulation options," as well as liver toxicity and drug development difficulties, a "POSA would have had no reason to expect that a new AED [antiepileptic drug], selected from a new, untested class of compounds such as FAAs, would avoid these problems." *Id.* at 53–54.

As Petitioner points out, however (*see* Pet. Reply 17), "[t]o be particularly probative, evidence of unexpected results must establish that there is a difference between the results obtained *and those of the closest prior art*, and that the difference would not have been expected by one of ordinary skill in the art at the time of the invention." *Bristol-Myers Squibb v. Teva*, 752 F.3d at 977 (emphasis added).

In the present case, Patent Owner does not identify specifically any particular compound as being the closest prior art, nor does Patent Owner direct us to a specific comparison between lacosamide/Vimpat and such a compound. We find, therefore, that Patent Owner's assertions regarding unexpected results are entitled to little probative weight in our overall obviousness calculus.

b. Industry Praise

As evidence of industry praise, Patent Owner identifies statements in several journal articles. PO Resp. 52–53 (citing Exs. 2102, 2103, 2014).[16,17,18] In each instance, however, we find that, at least at the time those articles were published, the authors' praise was somewhat tempered, describing their findings as preliminary in nature, with a desire for further confirmatory study. *See* Ex. 2102, 13 (citation omitted, emphasis added):

> Lacosamide has many favourable attributes, which *may* make it an optimal antiepileptic therapy, namely high oral efficacy, good tolerability, once or twice-daily dosing and minimal drug interactions. *However, while the efficacy of lacosamide appears to be promising, clinical data and experience with lacosamide are still lacking, compared with other antiepileptic agents. Therefore, further investigation is required to elucidate its importance fully in the treatment of patients with treatment-refractory focal-onset seizures.*

The relevant discussion in Exhibit 2103 is similar (citation omitted, emphasis added):

> Properties of an ideal AED include high oral efficacy, good tolerability, once- or twice-daily closing, minimal drug interactions, and no seizure aggravation or teratogenicity. . . . Clinical trials to date have demonstrated that lacosamide *might meet* these clinical criteria. In preclinical trials lacosamide was

[16] Juan Luis Becerra et al., *Review of Therapeutic Options for Adjuvant Treatment of Focal Seizures in Epilepsy[,] Focus on Lacosamide*, 25 CNS Drugs 3–16 (Supp. 1 2011) (Ex. 2012).

[17] Elinor Ben-Menachem et al., *Efficacy and Safety of Oral Lacosamide as Adjunctive Therapy in Adults with Partial-Onset Seizures*, 48 Epilepsia 1308–1317 (2007) (Ex. 2103).

[18] Stefano de Biase et al., *Lacosamide for the treatment of epilepsy*, 10 Expert Opin. Drug Metab. Toxicol. 459–468 (2014) (Ex. 2104).

> not teratogenic, *however, this can only be confirmed with experience in humans*. This trial demonstrated that twice daily dosing of lacosamide produced statistically significant reductions in seizure frequency at doses of 400 and 600 mg/day in patients with uncontrolled partial-onset seizures; however, the 400 mg/day dose of lacosamide was better tolerated than the 600 mg/day dose. These results suggest that lacosamide *has the potential* to become an effective pharmacological treatment option for patients with partial-onset seizures.

Ex. 2103, 1315–1316.

The relevant discussion in Exhibit 2104 is also similar (emphasis added):

> Clinical trials are evaluating the efficacy and safety of LCM [lacosamide] in subjects with partial-onset seizures. Current literature supports a well-definite role of LCM as adjunctive therapy for partial onset seizures; *however, its role as a monotherapy needs to be established*. In addition, there is a clinical trial with CBZ-CR, the efficacy and safety of LCM as a monotherapy in the treatment of partial-onset seizures and generalized tonic-clonic seizures. *If the efficacy of LCM is confirmed in both seizure types, this could markedly increase the use of LCM in the treatment of epilepsy in the next years.*

Ex. 2104, 465.

In sum, although we recognize that lacosamide has elicited praise in the field of epilepsy treatment, the tempered nature of the statements, seen above, reduces the probative weight of that evidence in our overall obviousness determination.

c. Skepticism; Failure of Others

Patent Owner submits a series of letters (Exs. 2141–2170) in support of its contentions that "[d]ozens of pharmaceutical companies turned down

the opportunity to take a license as a development partner for either FAAs generally or lacosamide specifically. . . . These refusals were based on skepticism about safety, efficacy, pharmacokinetics, and/or pharmacodynamics of the compounds." PO Resp. 54 (citing Exs. 2141–2170; Ex. 2132 ¶¶ 41–42 (Vellturo Decl.)) Patent Owner further contends that the only pharmaceutical company to take a chance on Dr. Kohn's FAA's was Eli Lilly ("Lilly"), but Lilly abandoned the project altogether after finding that one FAA exhibited severe liver toxicity and declined to take a license even after the specific lacosamide compound was discovered. *Id.* at 55 (citing Exs. 2069, 2125, 2157; Ex. 2036 ¶¶ 42, 314).

We agree with Petitioner (Pet. Reply 26), that Patent Owner fails to provide adequate context for the letters submitted as Exhibits 2141–2170. In particular, Patent Owner does not provide evidence explaining, as to any of the letters, what specific data had been presented to the potential licensees. Moreover, although Patent Owner asserts that the refusals were based on "skepticism about safety, efficacy, pharmacokinetics, and/or pharmacodynamics of the compounds" (PO Resp. 54), a majority of letters do not specifically mention any of those concerns. *See* Exs. 2141–2144, 2148, 2150–2154, 2158–2160, 2163, 2165, 2168, 2169.

As to Patent Owner's contentions regarding Lilly (PO Resp. 55 (citing Exs. 2125, 2157)), although the letter from Lilly expressed concern regarding lacosamide's results in a particular toxicity test, Lilly based its decision not to pursue the compound further on a lack of desire to perform extensive additional testing. Ex. 2157. Rather than expressing skepticism,

Lilly actually stated that it remained "very interested in developing drugs such as Harkeroside." *Id.* [19]

In sum, given the absence of evidence as to the specific data that was presented to the potential licensees mentioned in the letters, as well as the fact that a significant number of the letters did not specifically evince skepticism as to whether the discussed compounds would be useful as anticonvulsants, we accord little probative weight to the evidence of skepticism advanced by Patent Owner.

As to the failure of others, Patent Owner contends that the development of antiepileptic drugs in general is characterized by failures, as evidenced by the low percentage of screened compounds ultimately being approved by the FDA. PO Resp. 55 (citing Ex. 2036 ¶¶ 310–312 (Roush Decl.)). In this regard, Patent Owner contends that, even after FDA approval, several drugs were found to have serious side effects. *Id.* (citing Ex. 2038 ¶¶ 92–94 (Bazil Decl.)).

We acknowledge that antiepileptic drug development includes many failures, and also acknowledge evidence discussed below supporting Patent Owner's assertion that Vimpat addresses a previously unmet need in a particular set of epilepsy patients. Nonetheless, Patent Owner's witness, Dr. Vellturo, testifies that, as of the introduction of Vimpat in 2009, "the [antiepileptic drug] marketplace consisted of numerous suppliers, with many common drugs available at low cost from multiple generic providers." Ex. 2132 ¶ 14. Dr. Vellturo lists at least 15 drugs that have been approved for treating epilepsy. *Id.* In light of Dr. Vellturo's testimony, we are not

[19] According to Dr. Vellturo, the compound "Harkeroside" discussed in Exhibit 2157 is lacosamide. Ex. 2132 ¶ 42 (Vellturo Decl.).

persuaded that others have failed to develop antiepileptic drugs, despite any low rate of success of products that ultimately gain FDA approval.

d. Long-felt, But Unmet Need

Having reviewed the parties' contentions and supporting evidence on this issue, we agree with Patent Owner (PO Resp. 56–58) that lacosamide satisfied a long-felt but unmet need in that lacosamide has been found to be useful for treating refractory patients for which other antiepileptic drugs were ineffective. Patent Owner's witness on this issue, Dr. Bazil,[20] testifies as follows:

> For many of my patients, lacosamide is a very important option, and it certainly fills a need in those patients who require a drug with the unique combination of properties as lacosamide possesses. Thus, lacosamide exhibits its biggest advantages in refractory patients. I have had numerous patients who were able to successfully control their seizures with lacosamide, but who had failed to do so previously with other antiseizure drugs. As director of Columbia's Epilepsy Center, I have also heard many success stories from other neurologists about patients whose seizures were not controlled by other AEDs but were controlled when they switched to lacosamide.

Ex. 2038 ¶ 79 (Bazil Decl.).

The testimony as to this issue of Petitioner's witness, Dr. Davis,[21] is consistent with Dr. Bazil's:

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[20] Given Dr. Bazil's education and experience (Ex. 2038 ¶¶ 2, 4–14 (Bazil Decl.); Ex. 2039 (Dr. Bazil's curriculum vitae)), we credit his testimony on the matters for which Patent Owner advances his testimony.

[21] Dr. Kathryn A. Davis, a clinical epileptologist (epilepsy specialist) with over seven years of experience treating patients, and multiple medical board certifications, is Associate Director of the Penn Epilepsy Center and also serves as Medical Director of the Epilepsy Monitoring Unit and Epilepsy Surgical Program at Penn. Ex. 1087 ¶¶ 6–11.

> So, similar to Dr. Bazil, I actually have never used lacosamide as a first-line agent, or he said he rarely does, I believe, in his declaration.
>
> But – so when I've used lacosamide, it is typically in the setting of multiple prior antiepileptic drug failures, and a balance of side effects and efficacy for a given patient, similar to any other antiepileptic drug choice that I would make in my practice.

Ex. 2195, 53 (Davis Deposition).[22]

Petitioner does not dispute that lacosamide is effective in a subset of patients for which other antiepileptic drugs are not effective, but asserts that "that narrow starting point undermines the alleged need. The claims are not limited to AEDs [antiepileptic drugs] nor to AEDs that have minimal side effects." Pet. Reply 19.

We acknowledge that claims 1–9, which Petitioner does not dispute encompass lacosamide, are directed to chemical compounds rather than specific drug compositions or methods of treating specific patients. That fact does not persuade us, however, that the evidence regarding meeting a long-felt is not probative as to the obviousness of claims 1–9. *See In re Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011) (Although "[e]vidence of secondary considerations must be reasonably commensurate with the scope of the claims. . . [t]his does not mean that an applicant is required to test every embodiment within the scope of his or her claims."); *see also In re Chupp*, 816 F.2d 643, 645–46 (Fed. Cir. 1987) (evidence of unexpectedness as to particular use of chemical compounds recited in claims at issue considered

[22] Deposition of Kathryn A. Davis, M.D., December 14, 2016 (Ex. 2195) ("Davis Deposition"). In citing to the Davis Deposition, we cite to page numbers appearing at the top right portion of each page.

probative evidence of nonobviousness despite claims at issue not being limited to that specific use).

That lacosamide has not been approved for widespread use in epilepsy patients (*see* Pet. Reply 18–21) also does not persuade us that lacosamide's effectiveness failed to satisfy a long-felt need in patients for whom other drugs were not effective. As Patent Owner contends, and Petitioner does not dispute, investigators have sought, for decades at least, to uncover effective drugs for treating epilepsy. *See* PO Resp. 7, and exhibits cited therein. Petitioner's witness, Dr. Wang, agrees that the need has been largely unmet:

> Q. And Dr. Wang, is there an unmet need in epilepsy?
>
> A. Oh, absolutely.

Ex. 2035, 71 (First Wang Deposition).[23]

Thus, that lacosamide is effective in a subset of patients for which other antiepileptic drugs are not effective, is evidence that lacosamide satisfied a long-felt, but unmet need, which is a significant objective indicium of nonobviousness. *See Graham v. Deere*, 383 U.S. at 17; *Transocean v. Maersk*, 699 F.3d at 1347, 1353–54.

Lastly, as to Petitioner's contentions (Pet. Reply 21–22) that levetiracetam/Keppra, a distinct antiepileptic drug, had already satisfied the need satisfied by lacosamide, Petitioner does not identify any specific evidence suggesting that levetiracetam was effective in treating the same subset of refractory epilepsy patients for which lacosamide has been shown, on this record, to be useful.

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[23] Deposition of Dr. Binge Wang, Ph.D., July 18, 2016 (Ex. 2194) ("First Wang Deposition"). In citing to the First Wang Deposition, we cite to page numbers appearing at the top right portion of each page.

e. Commercial Success

Having reviewed the parties' contentions and supporting evidence, we agree with Patent Owner that Vimpat, the commercial embodiment of claims 1–9, is a commercial success. As discussed below, however, the probative weight of that success as to the ultimate conclusion of obviousness is undercut somewhat by the fact that the '301 and '729 patents also cover Vimpat.

As Patent Owner contends, and Petitioner does not dispute, since its introduction in 2009, Vimpat has generated more than $2.4 billion in net U.S. sales, and Vimpat's sales have increased significantly each year. PO Resp. 58 (citing Ex. 2132 ¶¶ 8, 17 (Vellturo Decl.)). As Patent Owner contends, and Petitioner does not dispute, 3.5 million total prescriptions have been written for Vimpat through February 2015, and prescriptions for Vimpat in the U.S. have risen from 300,000 in 2010 to 950,000 in 2014. PO Resp. 58 (citing Ex. 2132 ¶ 23).

Our reviewing court has explained that, "[w]hen 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). Once a patentee makes the required showing, "the burden shifts to the challenger to prove that the commercial success is instead due to other factors extraneous to the patented invention, such as advertising or superior workmanship." *Id.*

Petitioner does not dispute that claims 1–9 encompass Vimpat. Rather, Petitioner contends initially that the presumed nexus between

Vimpat's sales and claims 1–9 of the '551 patent is rebutted by the fact that Vimpat is covered by the claims of the earlier-issued '301 and '729 patents, which blocked market access. Pet. Reply 23 (citing *Merck & Co. v. Teva Pharms. USA*, 395 F.3d 1364, 1377 (Fed. Cir. 2005); *Galderma Labs v. Tolmar, Inc.*, 737 F.3d 731, 740–41 (Fed. Cir. 2013); *McNeil-PPC v. Perrigo*, 516 F. Supp. 2d 238, 254–55 (S.D.N.Y. 2007)).

We discern no *per se* rule from the cases Petitioner cites. Nonetheless, Patent Owner does not dispute that, like the situation in each of the cases cited by Petitioner, the '301 and '729 patents both cover Vimpat.

Unlike the situation in both *Merck v. Teva* and *Galderma v. Tolmar*, however, the claims of the '301 and '729 patents cover numerous compounds and do not recite lacosamide specifically. *See* Ex. 1019, 88:2–94:21 (claims of '301 patent); *see also* Ex. 1009, 61:40–76:25 (claims of '729 patent). In contrast, the claims of the blocking patents in *Merck* and *Galderma* specifically recited the same compound that was recited in the later-issued claims. *See Merck*, 395 F.3d at 1377; *Galderma*, 737 F.3d at 740–41.

Also different from the present situation, in both *Merck* and *McNeil-PPC*, factors in addition to the presence of blocking patents obstructed market entry. *See Merck*, 395 F.3d at 1377 (FDA marketing approval gave patentee exclusive right of sale); *see also McNeil-PPC*, 516 F. Supp. 2d at 254–55 (prior branding, significant advertising, withdrawal of similar-branded product just prior to patented product's introduction, also contributed to undercutting commercial success).

In sum, because the claims of the '301 and '729 patents undisputedly cover Vimpat, Petitioner persuades us that the presumption of nexus

between Vimpat and claims 1–9 of the '551 patent is significantly undercut. *See Merck*, 395 F.3d at 1377; *Galderma*, 737 F.3d at 740–41. Nonetheless, because the claims of the '301 and '729 patents do not recite lacosamide specifically, we decline to discard the entire probative weight of the evidence of commercial success on this basis.

As to Petitioner's assertion that Vimpat's approximately 4% share of the antiepileptic drug market is insufficient to show commercial success (Pet. Reply 24–25), we note, as Petitioner concedes, that Vimpat is only approved for use in a subset of adult epilepsy patients. *See* Pet. Reply 19 (citing Ex. 1087 ¶¶ 19–20 (Davis Decl.)). We note also, as Patent Owner contends (PO Resp. 58), and Petitioner does not dispute, that the antiepileptic drug market includes several well-established and low-priced generic alternatives. *See* Ex. 2132 ¶¶ 8, 13–14, 25 (Vellturo Decl.). Petitioner does not persuade us, therefore, that Vimpat's relatively small market share detracts from the probative value of its upward-trending sales and prescriptions, and significant overall sales.

Petitioner contends Patent Owner's evidence of commercial success is undercut by the fact that "[t]otal Vimpat sales may not even exceed costs incurred to date; thus, there may be no profit." Pet. Reply 25 (citing Ex. 1086 ¶¶ 22–27 (McDuff Decl.)). Petitioner does not, however, direct us to controlling law suggesting that commercial success demonstrated by significant sales in a relevant market, shown by Patent Owner as discussed above, is necessarily undercut by a lack of profitability in the initial years after a product's introduction, particularly in an industry such as that involved here, where the cost of commercialization can be extremely high.

See Ex. 1086 ¶ 25 (Dr. McDuff testifying that likely cost of commercialization of Vimpat was $2.6 billion, based on comparable drugs).

Petitioner asserts that Patent Owner's aggressive marketing weighs against the evidence of commercial success, particularly given Patent Owner's unique interest in filling the profit gap resulting from expiration of its Keppra patent. Pet. Reply 25–26 (citing Ex. 1086 ¶¶ 44–47, 51–56 (McDuff Decl.); Ex. 1087 ¶¶ 178–79 (Davis Decl.)). We are not persuaded.

As Patent Owner contends (PO Resp. 60), despite the rise in sales discussed above, Vimpat's marketing spend/sales ratio has trended downward and is comparable to other antiepileptic drugs. Ex. 2132 ¶¶ 17, 33 (Vellturo Decl.). Although Dr. McDuff testifies that the marketing spend/sales ratio metric relied upon by Dr. Vellturo has certain shortcomings (Ex. 1086 ¶¶ 55–56), Petitioner does not direct us to specific persuasive evidence controverting Dr. Vellturo's assertion (Ex. 2132 ¶ 33, n.10) that the methodology he employed is commonly used to perform such comparisons in the pharmaceutical industry.

In sum, for the reasons discussed, although we find that the commercial embodiment of claims 1–9 of the '551 patent, Vimpat, enjoyed commercial success, we find the probative weight of that success is undercut by the fact that the previously issued '301 and '729 patents also covered Vimpat. Nonetheless, as also discussed above, given the totality of the record as to commercial success, we conclude that the evidence of commercial success is entitled to weight in our overall evaluation of the obviousness of claims 1–9.

f. Copying

Patent Owner contends that "*sixteen* generic drug companies had the option to copy other AEDs, including AEDs that Petitioner argues have satisfied the need for AEDs. *See* [Pet. 54.] But instead, each of these generic companies sought approval for lacosamide." PO Resp. 60.

Patent Owner's factual basis for this specific assertion is unclear, as page 54 of the Petition does not appear to make any specific reference to generic drug companies. *See* Pet. 54. Nonetheless, we note that, in addressing Patent Owner's contentions regarding copying, Petitioner refers to a "wave of ANDA filings." Pet. Reply 27.

As our reviewing court has explained, "evidence of copying in the ANDA context is not probative of nonobviousness because a showing of bioequivalence is required for FDA approval." *Bayer Healthcare Pharm., Inc. v. Watson Pharm., Inc.*, 713 F.3d 1369, 1377 (Fed. Cir. 2013). We, therefore, assign no probative weight to Patent Owner's assertions of copying.

6. Conclusion of Obviousness for Claims 1–9

In sum, for the reasons discussed above, having considered the parties' contentions and supporting evidence as to the level of ordinary skill in the art, the scope and content of the prior art, and the differences between the prior art and claims 1–9 of the '551 patent, we find that the evidence of record does not support Petitioner's contention that an ordinary artisan would have been motivated to make the specific substitution to Kohn 1991's compound 3l, required to arrive at lacosamide. For the reasons discussed above, we find also that lacosamide satisfied a long-felt but unmet need, and that the evidence of commercial success is entitled to probative weight.

Accordingly, viewing all of the evidence regarding obviousness together, we conclude that Petitioner has not shown by a preponderance of the evidence that the compounds recited in claims 1–9 of the ’551 patent would have been obvious to an ordinary artisan in view of Kohn 1991 and Silverman.

D. Obviousness—Dependent claims 10–13

Each of claims 10–13 of the ’551 patent depends directly or ultimately from claims 1–9. Ex. 38:41–51. Claim 10 recites a therapeutic composition containing a compound as recited in any one of claims 1–9, and claims 11–13 recite methods of treating a central nervous system disorder by administering any one of the compounds of claims 1–9. *Id.*

Petitioner contends that the composition and methods recited in claims 10–13 would have been obvious in view of Kohn 1991, Silverman, and the ’729 patent. Pet. 48.

Petitioner’s challenge to claims 10–13, in its entirety, states: “Kohn 1991 and Silverman render obvious each of claims 1–9. Dependent claims 10–13 are obvious over Kohn 1991, Silverman, and the ’729 patent, based on the same rationales and prior art disclosures discussed in Ground 1B above. *See also* Claims Chart in Part XII below.” *Id.*

Patent Owner contends that Petitioner’s challenge to claims 10–13 is deficient in that the referenced Ground 1B concerns patentability over the combination of the LeGall Thesis and the ’729 patent and, thus, is “directed to a reference that is not at issue here.” PO Resp. 45.

Our reviewing court has explained that, “while the PTO has broad authority to establish procedures for revisiting earlier-granted patents in IPRs [*inter partes* reviews], that authority is not so broad that it allows the PTO to raise, address, and decide unpatentability theories never presented by

the petitioner and not supported by record evidence." *In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1381 (Fed. Cir. 2016).

In *Magnum Oil*, the court held that the Board improperly concluded that the petitioner had made a sufficient showing of obviousness, because the appealed ground of unpatentability included only conclusory statements that the claims at issue would have been obvious applying "'[t]he same analysis'" relied on elsewhere in the petition, the referenced analysis discussing a different combination of references. *Id.* at 1380. The court noted, in particular, that the analysis referenced in the appealed ground did not include specific discussion explaining why the particular combination of references cited in the appealed ground would have rendered obvious the claims at issue. *Id.* The court concluded that "[b]ecause such conclusory statements cannot satisfy the petitioner's burden of demonstrating obviousness, the Board did not have sufficient evidence on which to base its legal conclusion of obviousness." *Id.*

In the present case, similar to *Magnum Oil*, Petitioner's challenge to claims 10–13 states that the claimed subject matter would have been obvious "based on the same rationales and prior art disclosures discussed in Ground 1B above." Pet. 48. Similar to *Magnum Oil*, Petitioner's Ground 1B is not based on the same combination of references asserted in the instituted ground at issue here (Kohn 1991, Silverman, and the '729 patent), but is instead based on the combination of the LeGall Thesis and the '729 patent, a combination for which trial was not instituted. *See* Pet. 25–34 (Ground 1B); *see also* Dec. 12 (declining to institute as to Ground 1B).

Also similar to *Magnum Oil*, Ground 1B includes no specific discussion explaining why an ordinary artisan would have combined

Kohn 1991, Silverman, and the ’729 patent, but instead only explains why the combination of the LeGall Thesis and the ’729 patent would have rendered claims 10–13 obvious. *See* Pet. 25–34. Although the ground at issue here also references the claim chart in Part XII of the Petition, that chart also includes no mention of either Kohn 1991 or Silverman. *See* Pet. 58–59.

Accordingly, as in *Magnum Oil*, because Petitioner’s ground of unpatentability based on the combination of Kohn 1991, Silverman, and the ’729 patent does not provide specific discussion explaining why an ordinary artisan would have combined those references to arrive at the subject matter recited in claims 10–13 of the ’551 patent, and because that ground is instead based on a conclusory assertion referencing a distinct ground of unpatentability discussing a different combination of references, we conclude that Petitioner has not advanced sufficient argument and evidence on which a legal conclusion of obviousness may be based. Moreover, even if we were to conclude (which we do not) that *Magnum Oil* does not govern the present fact situation, Petitioner does not direct us to specific persuasive evidence suggesting that the combination of Kohn 1991, Silverman, and the ’729 patent undermines our conclusion that Petitioner fails to establish obviousness sufficiently, discussed above, in relation to the compounds of claims 1–9, which compounds are required by each of claims 10–13. *See In re Fine*, 837 F.2d 1071, 1076 (Fed. Cir. 1988) (“Dependent claims are nonobvious under section 103 if the independent claims from which they depend are nonobvious.”).

In sum, for the reasons discussed, we conclude that Petitioner has not shown by a preponderance of the evidence that claims 10–13 of the ’551

patent would have been obvious based on the combination of Kohn 1991, Silverman, and the ’729 patent.

IV. MOTIONS TO EXCLUDE

A. Petitioner’s Motion to Exclude

1. Exhibits 2125 and 2141–2170

Petitioner moves to exclude Exhibits 2125 and 2141–2170 based on lack of authentication under Federal Rule of Evidence (FRE) 901, as hearsay under FRE 801 and 802, under FRE 106 for incompleteness, and based on Patent Owner’s alleged failure to comply with the Board’s discovery rules. Pet. Mot. Exclude 2–7. We deny Petitioner’s motion to those exhibits.

As discussed above, Exhibits 2125 and 2141–2170 are letters advanced by Patent Owner to show skepticism in the industry, based on the fact that a number of pharmaceutical companies declined to license the technology involved in the claims of the ’551 patent. As also discussed above, we found that the letters provide little probative weight on that issue.

In any event, Petitioner fails to explain adequately why the declarations of Patent Owner’s President, Shaun Kirkpatrick (Ex. 2185), and Vice President and General Counsel of a licensee, Paul Petigrow (Ex. 2187), are insufficient to authenticate the letters. Although Petitioner contends that “[n]either declaration demonstrates personal knowledge of the facts necessary to establish the business-records exception” (Pet. Reply Opp. 1 (Paper 81)), Petitioner does not support that assertion with specific explanation, other than asserting that Mr. Petigrow has worked for the licensee for less than a year (*see id.*). Petitioner does not, however, address with any specificity the substance of any of Mr. Petigrow’s other assertions, nor does Petitioner explain why they should not be credited.

As to hearsay, as Patent Owner contends (PO Opp. 5–6), under FRE 703, the proponent of an expert opinion may disclose otherwise inadmissible evidence underlying that opinion to a jury, if the court determines that the "probative value in helping the jury evaluate the opinion substantially outweighs [its] prejudicial effect." In the present case, Patent Owner's expert Dr. Roush relied on Exhibit 2125 (*see* Ex. 2036 ¶ 314 (Roush Decl.)), and another expert witness, Dr. Vellturo, relied on Exhibits 2141–2170 (*see* Ex. 2132 ¶¶ 41–42 (Vellturo Decl.)). As is evident from our discussion above, the probative value of reviewing the documents substantially assisted our evaluation of Patent Owner's contentions regarding skepticism. In addition, any prejudicial effect on Petitioner is minimal because we ultimately did not find Patent Owner's evidence of skepticism to be probative.

Lastly, we are not persuaded that Patent Owner's alleged failure to submit controverting correspondence warrants exclusion of Exhibits 2125 and 2141–2170 under either FRE 106 or the Board's discovery rules. FRE 106, which appears to be more pertinent to a live trial, as opposed to an administrative proceeding such as this case, provides that "[w]hen a writing or recorded statement or part thereof is introduced by a party, an adverse party may require the introduction at that time of any other part or any other writing or recorded statement which ought in fairness to be considered contemporaneously with it."

Thus, rather than providing a basis for excluding evidence, FRE 106 is a vehicle for entry of additional evidence, allowing an adverse party to a proffered writing or statement (in this case Petitioner) the opportunity to require entry of any other part of the proffered writing/statement, or any

other writing or recorded statement, which should be considered contemporaneously with the proffered writing/statement, based on fairness. As to the assertion that the alleged failure to comply with the Board's discovery rules affords exclusion in this instance, that the evidence adduced during the copending district court proceeding might not be entirely contiguous with the evidence presented here does not persuade us that Patent Owner failed to comply with the relevant discovery rules.

In sum, for the reasons discussed, we deny Petitioner's motion to exclude Exhibits 2125 and 2141–2170.

2. Exhibits 2174–2180

Petitioner moves to exclude Exhibits 2174–2180 under FRE 106 for incompleteness, and based on Patent Owner's alleged failure to comply with the Board's discovery rules. Pet. Mot. Exclude 7–10. We deny Petitioner's motion to exclude those exhibits.

Exhibits 2174–2180 are documents disclosing a variety of information, such as sales figures for Vimpat, as well as calculations based on that information relied upon by Dr. Vellturo in his economic analysis in relation to Vimpat. *See, e.g.*, Ex. 2132 ¶¶ 17, 19, 32; *see also* Exs. 2174–2180.

As discussed above, Petitioner does not persuade us that FRE 106 provides a basis for excluding evidence, but instead is a vehicle for introducing evidence that should be fairly considered alongside a proffered writing or statement. As also discussed above, that the evidence adduced during the copending district court proceeding might not be entirely contiguous with the evidence presented here does not persuade us that Patent

Owner failed to comply with the relevant discovery rules, to an extent warranting exclusion of Exhibits 2174–2180.

For the reasons discussed, we deny Petitioner's motion to exclude Exhibits 2174–2180.

3. Exhibits 2181 and 2182

As Petitioner explains, Exhibits 2181 and 2182 are the District Court's Order and Memorandum Opinion in *UCB, Inc. et al. v. Accord Healthcare Inc. et al.*, 1:13-cv-01206-LPS (D. Del. August 12, 2016), the copending District Court proceeding involving the '551 patent. Pet. Mot. Exclude 10. Petitioner contends that Exhibits 2181 and 2182 lack relevance because the court's decision is based on different evidence and stipulated facts that are disputed in this proceeding. *Id.*

We have independently considered the contentions and supporting evidence advanced by the parties in this proceeding, and do not rely on the findings or conclusions in the District Court's opinion. Accordingly, because our decision herein does not rely on Exhibits 2181 and 2182, we dismiss as moot Petitioner's Motion to Exclude as to those exhibits.

B. Patent Owner's Motion to Exclude

1. Exhibit 1003

Patent Owner moves to exclude Exhibit 1003 as inadmissible hearsay under FRE 801(c) and FRE 802. PO Mot. Exclude 2–3.

Exhibit 1003 is the Declaration of Dr. Clayton Heathcock, submitted in support of the petition in a prior proceeding, IPR2014-001126, challenging the claims of the '551 patent. *See* Ex. 1003. Because we do not rely on Exhibit 1003 in our decision, we dismiss as moot Patent Owner's Motion to Exclude as to Exhibit 1003.

2. Exhibits 1048–1213

Patent Owner moves to exclude Exhibits 1048–1213, all of the exhibits submitted with Petitioner's Reply, "because they were not served on Patent Owner with the Reply as required by 37 C.F.R. § 42.51(b)(1)(i)." PO Mot. Exclude 3. In particular, Patent Owner contends that the exhibits were one day late, and that the lateness was prejudicial, given the volume of documents and the time needed to serve evidence objections and prepare for cross-examination. *Id.* at 4–5; *see also* PO Reply Opp. 2 (Paper 80) ("It is undisputed that Petitioners filed Exhibits 1048–1213 with the Board on November 14, 2016, but they did not even attempt service of Exhibits 1048–1213 until the next day.").

Having considered the parties' contentions and supporting evidence on this issue we conclude that, in light of the relatively short delay between filing and service, exclusion of every exhibit filed with Petitioner's Reply would be an excessive remedy. Moreover, as Petitioner points out (Pet. Opp. 5 (Paper 78)), 37 C.F.R. § 42.5(c)(3) states that "[a] late action will be excused on a showing of good cause or upon a Board decision that consideration on the merits would be in the interests of justice." We conclude that considering Exhibits 1048–1213 is in the interests of justice in deciding the merits of the parties' contentions in this proceeding.

In sum, for the reasons discussed, we deny Patent Owner's Motion to Exclude Exhibits 1048–1213 on this basis.

3. Exhibit 1050 (Roush Deposition)

Patent Owner moves to exclude the cross-examination testimony of Dr. Roush relating to the '301 patent. PO Mot. Exclude 5–6. Patent Owner contends that Dr. Roush's Declaration did not include testimony as to the

’301 patent, and, therefore, his deposition testimony relating to the ’301 patent is outside the scope of proper cross-examination under 37 C.F.R. § 42.53(d)(5)(ii). PO Mot. Exclude 5–6.

The obviousness ground relating to claims 1–9, however, did include a citation to the ’301 patent. *See* Pet. 46–47. Given that Dr. Roush’s testimony, as discussed above, was advanced to rebut that obviousness ground, we conclude that it was not outside the proper scope of cross-examination to question Dr. Roush about the ’301 patent. We, therefore, deny Patent Owner’s Motion to Exclude the cited portions of Dr. Roush’s cross-examination testimony.

4. Exhibit 1104

Patent Owner moves to exclude Exhibit 1104 under FRE 901 because of lack of authentication, and under FRE 1001(e) and FRE 1003, as an inappropriate duplicate. PO Mot. Exclude 6–8.

Exhibit 1104 is a compilation of PI values of compounds in the prior art of record, relied upon by Dr. Wang in his Reply Declaration. *See* Ex. 1084 ¶¶ 96, 234 (Wang Reply Decl.); *see also* Ex. 1104.

As discussed above, under FRE 703, the proponent of an expert opinion may disclose otherwise inadmissible evidence underlying that opinion to a jury, if the court determines that the “probative value in helping the jury evaluate the opinion substantially outweighs [its] prejudicial effect.” We conclude that the ability to evaluate the document underlying Dr. Wang’s testimony outweighs any prejudicial effect Exhibit 1104 might engender. We, therefore, deny Patent Owner’s Motion to Exclude Exhibit 1104 on this basis.

5. Exhibits 1156 and 2035

Patent Owner moves to exclude Exhibit 1156 under FRE 402 as lacking relevance and under 37 C.F.R. § 42.123(c) as unauthorized evidence outside the scope of an instituted ground. PO Mot. Exclude 8–9.

Patent Owner also moves to exclude Exhibit 2035, 246:22–254:1, for similar reasons. PO Mot. Exclude 10–11.

Exhibit 1156 is the transcript of a deposition of Mr. John Lehner submitted in support of Petitioner's contention that the LeGall Thesis is available as prior art against the claims of the '551 patent. *See* Pet. Reply 27–28 (citing Ex.1156, 143:4–12). Exhibit 2035, 246:22–254:1, is the deposition testimony of Dr. Wang, on re-direct, in relation to the public availability of the LeGall Thesis. *See, e.g.*, Ex. 2035, 253.

As noted above, because Petitioner's contentions and supporting evidence in the Reply regarding the LeGall Thesis exceed the proper scope of a reply, our decision does not consider or rely on the arguments on pages 27–29 of the Reply regarding the LeGall Thesis, or the evidence advanced in support of those arguments, said evidence including Exhibit 1156 and the cited portions of Exhibit 2035. Because our decision does not rely on Exhibit 1156 or Exhibit 2035, 246:22–254:1, we dismiss as moot Patent Owner's Motion to Exclude those Exhibits.

6. Exhibit 1158

Patent Owner moves to exclude Exhibit 1158 under FRE 901 due to a lack of authentication. PO Mot. Exclude 11–12.

Exhibit 1158 is a series of tables containing antiepileptic drug information, including sales data, relied upon by Dr. McDuff in his Reply

Declaration. *See* Ex. 1086 ¶¶ 10, 17, 20, 26, 43, 56 (McDuff Decl.); *see also* Ex, 1158.

As discussed above, under FRE 703 the proponent of an expert opinion may disclose otherwise inadmissible evidence underlying that opinion to a jury, if the court determines that that the "probative value in helping the jury evaluate the opinion substantially outweighs [its] prejudicial effect." We conclude that the ability to evaluate the documents underlying Dr. McDuff's testimony outweighs any prejudicial effect Exhibit 1158 might engender. We, therefore, deny Patent Owner's Motion to Exclude Exhibit 1158 on this basis.

V. CONCLUSION

For the foregoing reasons, Petitioner has not established by a preponderance of the evidence that claims 1–9 of the '551 patent are unpatentable for obviousness over Kohn 1991 and Silverman, nor has Petitioner established by a preponderance of the evidence that claims 10–13 of the '551 patent are unpatentable for obviousness over Kohn 1991, Silverman, and the '729 patent.

VI. ORDER

It is ORDERED that claims 1–13 of the '551 patent have not been shown by a preponderance of the evidence to be unpatentable;

FURTHER ORDERED that Petitioner's Motion to Exclude is denied-in-part and dismissed-in-part as moot; and

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

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

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