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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

INCYTE CORPORATION,
Petitioner,

v.

CONCERT PHARMACEUTICALS, INC.,
Patent Owner.

Case IPR2017-01256
Patent 9,249,149 B2

Before ERICA A. FRANKLIN, TINA E. HULSE, and RICHARD J. SMITH, *Administrative Patent Judges*.

FRANKLIN, *Administrative Patent Judge*.

FINAL WRITTEN DECISION

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

I. INTRODUCTION

Incyte Corporation ("Petitioner") filed a Petition requesting an *inter partes* review of claims 1–15 of U.S. Patent No. 9,249,149 B2 (Ex. 1001, "the '149 patent"). Paper 1 ("Pet."). Concert Pharmaceuticals, Inc. ("Patent Owner") filed a Preliminary Response to the Petition. Paper 8 ("Prelim. Resp."). Initially, the Board denied institution of an *inter partes* review of those claims based upon all grounds asserted in the Petition, i.e., one anticipation and two obviousness grounds. Paper 9. Thereafter, Petitioner filed a Request for Rehearing relating to the two obviousness grounds asserted. Paper 12. The rehearing request was granted. Paper 13. On April 9, 2018, the Board instituted an *inter partes* review of claims 1–15 based upon one of the asserted obviousness grounds. Paper 14 ("Inst. Dec.").

On May 9, 2018, in view of *SAS Institute, Inc. v. Iancu*, 138 S. Ct. 1348 (2018), the Board modified the institution decision to include all of the challenged claims and all of the grounds asserted in the Petition. Paper 19. Subsequently, with Board authorization, the parties filed a Joint Motion to Limit the Petition, requesting that the Petition and *inter partes* review be limited to the two obviousness grounds asserted. Paper 20. The Board granted the joint motion and, thereby, removed the anticipation ground from this proceeding. Paper 21.

Thereafter, Patent Owner filed a Patent Owner Response to the Petition. Paper 27 ("PO Resp."). Petitioner filed a Reply to the Patent Owner Response. Paper 62 (sealed), Paper 70 (public), (collectively "Reply").[1] Patent Owner filed an Amended Sur-Reply to Petitioner's Reply

[1] The Board previously granted Patent Owner's Unopposed Motion for Entry of a modified version of the Default Standard Protective Order.

to Patent Owner's Response. Paper 85. Petitioner filed a Sur-Sur-Reply to Patent Owner's Amended Sur-Reply. Paper 89.

Patent Owner filed a Contingent Motion to Amend. Paper 44 ("Amend Mot."). Petitioner filed an Opposition to the Contingent Motion to Amend. Paper 63 (sealed), Paper 71 (public), (collectively, "Amend Opp."). Patent Owner filed an Amended Reply to Petitioner's Opposition to the Motion to Amend. Paper 84. Petitioner filed a Sur-Reply to Patent Owner's Reply to Opposition to Motion to Amend. Paper 93 (sealed), Paper 100 (public).

Petitioner filed a Motion for Additional Discovery. Paper 31. Patent Owner filed an Opposition to the Motion for Additional Discovery. Paper 33. Petitioner filed a Reply to the Opposition. Paper 42. We granted the motion, in part. Paper 54.

Petitioner also filed a Motion to Exclude. Paper 94 ("Exclude Mot."). Patent Owner filed an Opposition to the Motion to Exclude. Paper 102 ("Exclude Opp."). Petitioner filed a Reply to Patent Owner's Opposition. Paper 103.

Patent Owner filed a Motion to Submit Supplemental Information. Paper 105. Petitioner filed an Opposition to Patent Owner's Motion to Submit Supplemental Information. Paper 109 (sealed). We denied the motion. Paper 118.

Paper 16. The parties have filed a number of motions to seal, many of which are contested. The Board has addressed each of those motions. Papers 101 and 117.

On January 25, 2019, the parties presented arguments at an oral hearing. Paper 98. The hearing transcript has been entered in the record. Paper 113 ("Tr.").

We issue this Final Written Decision pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73. Having considered the record before us, we determine that Petitioner has shown by a preponderance of the evidence that claims 1–15 of the '149 patent are unpatentable. *See* 35 U.S.C. § 316(e). Additionally, we deny the Contingent Motion to Amend. We also decide the Motion to Exclude in this Final Written Decision.

A. Related Proceedings

The parties identify pending U.S. Patent Application No. 14/570,954 as a related matter to this proceeding. Pet. 1; Paper 5, 1. The '149 patent is a continuation of that application.

B. The '149 Patent

The '149 patent is entitled "Deuterated Derivatives of Ruxolitinib," and issued on February 2, 2016. Ex. 1001, [54], [45]. According to the '149 patent, many current medicines suffer from poor adsorption, distribution, metabolism, and/or excretion ("ADME") properties that limit their use for certain indications. *Id.* at 1:20–23. For example, rapid metabolism can cause drugs to be cleared too rapidly from the body, decreasing the drugs' efficacy in treating a disease. *Id.* at 1:28–31. Another ADME limitation is the formation of toxic or biologically reactive metabolites. *Id.* at 1:39–40.

The cytochrome P450 enzyme ("CYP") is typically responsible for hepatic metabolism of drugs. *Id.* at 1:52–54. As such, the '149 patent identifies deuterium modification as a "potentially attractive strategy for improving a drug's metabolic properties." *Id.* at 2:5–6.

Deuterium modification involves replacing one or more hydrogen atoms of a drug with deuterium atoms in an attempt to slow the CYP-mediated metabolism of a drug or to reduce the formation of undesirable metabolites. *Id.* at 2:6–10. Because deuterium forms stronger bonds with carbon than hydrogen, in certain cases, that stronger bond strength can positively impact the ADME properties of a drug, resulting in the potential for improved drug efficacy, safety, and/or tolerability. *Id.* at 2:11–15.

According to the '149 patent, however, studies measuring deuterium substitution's effect on overall metabolic stability have reported variable and unpredictable results. *Id.* at 2:32–35. The '149 patent explains that the effects of deuterium modification on a drug's metabolic properties are not predictable "even when deuterium atoms are incorporated at known sites of metabolism." *Id.* at 2:42–44. As such, the Specification states that determining whether and how deuterium modification affects the metabolism rate of a drug requires actually preparing and testing the deuterated drug. *Id.* at 2:44–47. Thus, the '149 patent states that "[t]he site(s) where deuterium substitution is required and the extent of deuteration necessary to see an effect on metabolism, if any, will be different for each drug." *Id.* at 2:49–52.

The Specification describes ruxolitinib phosphate as a heteroaryl-substituted pyrrolo [2,3-d]pyrimidine that inhibits Janus Associated Kinases 1 and 2 ("JAK1" and "JAK2"). Those "kinases mediate the signaling of a number of cytokines and growth factors important for hematopoiesis and immune function." *Id*. at 2:53–61. Ruxolitinib phosphate is an approved drug for treating patients with intermediate or high-risk myelofibrosis. *Id.* at 2:66–67. Other potential applications for the drug include treating essential

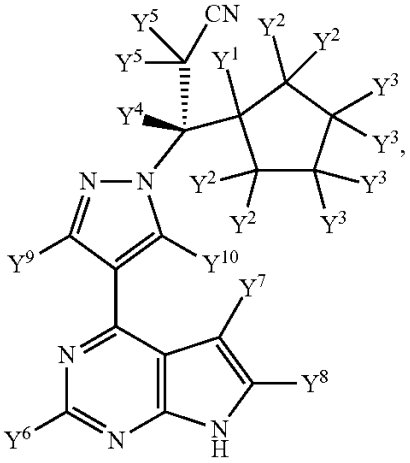
thrombocytopenia, psoriasis, and various forms of cancer. *Id.* at 3:3–6. Thus, according to the Specification, "[d]espite the beneficial activities of ruxolitinib, there is a continuing need for new compounds to treat the aforementioned diseases and conditions." *Id.* at 3:19–21.

C. Illustrative Claims

Petitioner challenges claims 1–15 of the '149 patent, of which claims 1 and 9 are the only independent claims. Claims 1 and 9 are illustrative and are reproduced below:

1. A compound of Formula A:

Formula A



or a pharmaceutically acceptable salt thereof, wherein:

Y^1 is a hydrogen;

each Y^2 is selected from hydrogen and deuterium, and each Y^2 is the same;

each Y^3 is selected from hydrogen and deuterium, and each Y^3 is the same;

Y^4 is selected from hydrogen and deuterium;

each Y^5 is the same and is selected from hydrogen and deuterium; and

Y^6, Y^7, Y^8, Y^9, and Y^{10} are each independently selected from hydrogen and deuterium; provided that:

each Y^2 is deuterium; or

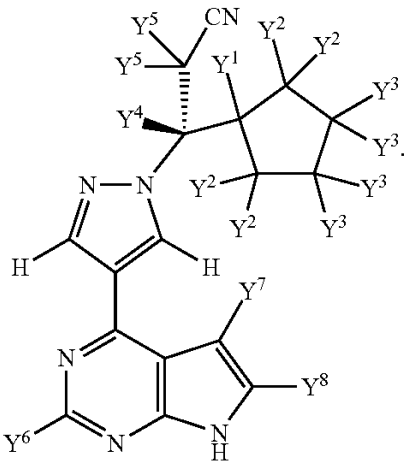
each Y^3 is deuterium; or

each Y^2 and each Y^3 is deuterium.

Ex. 1001, 36:17–53.

Claim 9 is similar to claim 1, except that it is directed to Formula I, which is reproduced below:

Formula I



Formula I is similar to Formula A, except that Y^9 and Y^{10} of Formula A are both hydrogen in Formula I.

Claims 2–7 and 10–14 depend from claim 1 or claim 9 and recite specific deuteration patterns of ruxolitinib. Claims 8 and 15 depend from claim 1 and claim 9, respectively, and recite a pharmaceutical composition of claim 1 or claim 9, and a pharmaceutically acceptable carrier.

D. Instituted Grounds of Unpatentability

Petitioner challenges the patentability of claims 1–15 of the '149 patent on the following two obviousness grounds:

References	Basis	Claims challenged
Rodgers,[2] Shilling,[3] and Concert Backgrounder[4]	§ 103	1–15
Jakafi Label,[5] Shilling, and Concert Backgrounder	§ 103	1–15

Petitioner also relies on the Declarations of F. Peter Guengerich, Ph.D. (Ex. 1002), Jerry Shapiro, M.D. (Ex. 1117), and Ronald A. Thisted, Ph.D. (Ex. 1129). Patent Owner relies on the Declarations of Scott Harbeson, Ph.D. (Ex. 2001 and Ex. 2071, sealed; Ex. 2079, public), Thomas B. Baille, Ph.D., D.SC. (Ex. 2002), Julian Mackay-Wiggan, M.D., M.S. (Ex. 2048), Paul Ortiz de Montellano, Ph.D. (Ex. 2057), and Dr. Cameron Cowden, Ph.D. (Ex. 2122, sealed; Ex. 2123, public).

II. ANALYSIS

A. Person of Ordinary Skill in the Art

The level of skill in the art is a factual determination that provides a primary guarantee of objectivity in an obviousness analysis. *Al-Site Corp. v.*

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[2] Rodgers et al., US 7,598,257 B2, issued Oct. 6, 2009 ("Rodgers," Ex. 1007).
[3] Shilling et al., *Metabolism, Excretion, and Pharmacokinetics of [^{14}C]INCB018424, a Selective Janus Tyrosine Kinase ½ Inhibitor, in Humans*, 38 DRUG METABOLISM AND DISPOSITION 2023–31 (2010) ("Shilling," Ex. 1005).
[4] CoNCERT Pharmaceuticals, Inc. PRECISION DEUTERIUM CHEMISTRY BACKGROUNDER ("Concert Backgrounder," Ex. 1006).
[5] Jakafi Prescribing Information (revised 11/2011) ("Jakafi Label," Ex. 1004).

VSI Int'l Inc., 174 F.3d 1308, 1324 (Fed. Cir. 1999) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966); *Ryko Mfg. Co. v. Nu-Star, Inc.*, 950 F.2d 714, 718 (Fed. Cir. 1991)).

Petitioner asserts that a person of ordinary skill in the art as of June 15, 2012, would have had a "master's degree or a Ph.D. in chemistry, biochemistry, pharmaceutics, pharmaceutical sciences, physical organic chemistry or a related discipline," or a lesser degree with more experience. Pet. 9 (citing Ex. 1002 ¶¶ 15–18). Patent Owner asserts that human drug development experience "is a necessary part of the POSA definition." PO Resp. 40. Accordingly, Patent Owner asserts the following definition for a person of ordinary skill in the art at the time of the invention:

> A person of ordinary skill in the art would typically have had a master's degree or a Ph.D. in chemistry, biochemistry, pharmaceutics, pharmaceutical sciences, physical organic chemistry or a related discipline. Alternatively, the person of ordinary skill in the art may have had a lesser degree in one of those fields, but accompanied by more experience. To the extent necessary, a person of ordinary skill in the art may have collaborated with others of skill in the art, such that the individual and/or team collectively would have had experience in synthesizing and analyzing complex organic compounds, developing drugs for human use, including analyzing human pharmacokinetic, pharmacodynamic, and ADME parameters and conducting and evaluating *in vitro* testing, human *in vivo* testing, and/or treating JAK1 or JAK2-mediated diseases and disorders in humans.

Id. at 39–40 (citing Ex. 2048 ¶ 5).

Based on the record as a whole, we determine that an appropriate description of the level of ordinary skill in the art incorporates Petitioner's definition with a portion of Patent Owner's definition, wherein,

> A person of ordinary skill in the art would typically have had a master's degree or a Ph.D. in chemistry, biochemistry, pharmaceutics, pharmaceutical sciences, physical organic chemistry or a related discipline. Alternatively, the person of ordinary skill in the art may have had a lesser degree in one of those fields, but accompanied by more experience. To the extent necessary, a person of ordinary skill in the art may have collaborated with others of skill in the art, such that the individual and/or team collectively would have had experience in synthesizing and analyzing complex organic compounds and developing drugs for human use.

We further note that the prior art itself demonstrates the level of skill in the art at the time of the invention. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (explaining that specific findings regarding ordinary skill level are not required "'where the prior art itself reflects an appropriate level and a need for testimony is not shown'" (quoting *Litton Indus. Prods., Inc. v. Solid State Sys. Corp*., 755 F.2d 158, 163 (Fed. Cir. 1985))).

B. Claim Construction

In an *inter partes* review, the Board interprets claim terms in an unexpired patent according to the broadest reasonable construction in light of the Specification of the patent in which they appear. 37 C.F.R. § 42.100(b) (2016); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2142 (2016) (affirming applicability of broadest reasonable construction standard to *inter partes* review proceedings).[6] Under that standard, and absent any

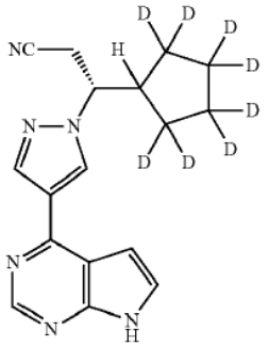
[6] A recent change to the claim construction standard for *inter partes* reviews does not apply here based on the filing date of the Petition. *See* Changes to the Claim Construction Standard for Interpreting Claims in Trial Proceedings Before the Patent Trial and Appeal Board, 83 Fed. Reg. 51,340 (October 11, 2018) (amending 37 C.F.R. § 42.100(b), effective Nov. 13, 2018).

special definitions, we generally give claim terms their ordinary and customary meaning, as would be understood by one of ordinary skill in the art at the time of the invention. *See In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). Any special definitions for claim terms must be set forth with reasonable clarity, deliberateness, and precision. *See In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

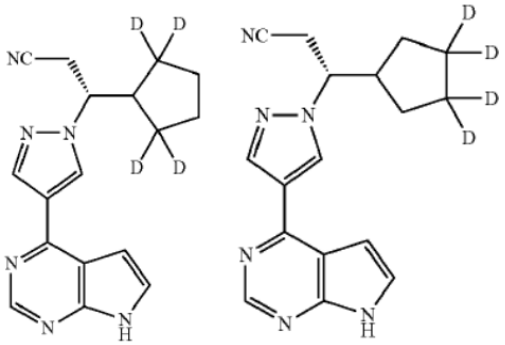
Petitioner asserts that the claim term "'D' or 'deuterium' is defined in the '149 [p]atent as meaning that the position has 'deuterium at an abundance that is at least 3000 times greater than the natural abundance of deuterium, which is 0.015% (i.e., at least 45% incorporation of deuterium).'" Pet. 24 (quoting Ex. 1001, 3:65–43). We recognize that Specification definition and accept it as the broadest reasonable construction for the term.

The parties do not assert that any other claim term requires express construction for purposes of this Decision. We agree. *See Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011) ("[C]laim terms need only be construed 'to the extent necessary to resolve the controversy.'" (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999)); *see also Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) (applying *Vivid Techs.* in the context of an *inter partes* review)).

We note, however, that Petitioner limits its analysis to three compounds that it contends are covered by each of the claims. Specifically, Petitioner asserts that claims 1, 2, 5–7, 9, 10, 13, and 14 each read on the following "octa-deuterated" ruxolitinib analog, which is reproduced below:



Pet. 8. The "octa-deuterated" ruxolitinib analog replaces each Y^2 and Y^3 hydrogen with deuterium. Petitioner also asserts that claims 1–4, 6, 7, 9–12, and 14 each read on the following "tetra-deuterated" ruxolitinib analogs, which are reproduced below:



Id. The "tetra-deuterated" ruxolitinib analogs replace each Y^2 or each Y^3 hydrogen with deuterium. Patent Owner asserts that "the challenged claims cover variations [of] deuterated compounds," but does not dispute Petitioner's contention that the above-described three compounds are covered by the claims. PO Resp. 39.

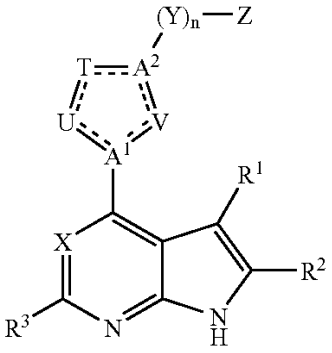
Having considered the compounds and the claims, we agree that the challenged claims encompass the three compounds as set forth by Petitioner.

C. Obviousness over Rodgers, Shilling, and Concert Backgrounder

Petitioner asserts that claims 1–15 are unpatentable as obvious over the combination of Rodgers, Shilling, and the Concert Backgrounder. Pet. 50–55. Patent Owner disagrees. PO Resp. 46–71.

1. Rodgers

Rodgers is a U.S. Patent directed to heteroaryl substituted pyrrolo[2,3-b]pyridines and heteroaryl substituted pyrrolo[2,3-b]pyrimidines that modulate the activity of Janus kinases and are useful in treating diseases related to the activity of Janus kinases. Ex. 1007, 1:18–22.[7] The compounds of Rodgers's invention have "Formula I," including pharmaceutically acceptable salt forms or prodrugs. *Id*. at 8:17–36. An illustration of Rodgers's Formula I is reproduced below:



Id. at 7:20–37. Rodgers's Formula I, reproduced above, includes numerous possibilities for each constituent member. *Id.* at 7:38–11:20. Rodgers states that its invention includes all stereoisomers, such as enantiomers and diastereomers (unless otherwise indicated). *Id.* at 31:32–34. Compounds of

[7] We use traditional patent citation for Rodgers and we cite to the original page numbers for Shilling and the Concert Backgrounder, rather than the page numbers assigned by Petitioner.

the invention also include "all isotopes of atoms occurring in the intermediates or final compounds. . . . For example, isotopes of hydrogen include tritium and deuterium." *Id.* at 32:13–17. Claims 1–3 recite ruxolitinib and its isomer. *Id.* at 374:12–20 (claims 1–3). Claim 4 recites a "composition comprising the compound of any one of claims 1 to 3 . . . and at least one pharmaceutically acceptable carrier." *Id*. at 374:21–23.

2. Shilling

Shilling teaches that ruxolitinib (INCB018424) is an orally active and "potent, selective inhibitor of Janus tyrosine kinase 1/2 and the first investigational drug of its class in phase III studies for the treatment of myelofibrosis." Ex. 1005, 2023. Shilling discloses a study of the metabolism, excretion, and pharmacokinetics of ruxolitinib. *Id.* In its study, Shilling identifies two major metabolites of ruxolitinib: M18 (2-hydroxycyclopentyl ruxolitinib) and M16/M27 (3-hydroxycyclopentyl ruxolitinib). *Id.* at 2030.

3. Concert Backgrounder

The Concert Backgrounder discloses the product platform of "CoNCERT Pharmaceuticals, Inc." Ex. 1006, 2. The Concert Backgrounder explains the potential benefits of deuterium modification, including improved safety, better tolerability, and enhanced efficacy. *Id.* at 3. The Concert Backgrounder states, however, that "the magnitude and nature of the deuterium benefit cannot be predicted *a priori*, [so] CoNCERT must test multiple compounds in a range of assays to identify those that are differentiated." *Id.*

4. Public Accessibility of the Concert Backgrounder

As an initial matter, we address Patent Owner's contention that Petitioner has failed to carry its burden of proving that the Concert Backgrounder is a prior art printed publication. PO Resp. 40.

Whether a particular reference qualifies as a printed publication "is a legal determination based on underlying fact issues, and therefore must be approached on a case-by-case basis." *In re Hall*, 781 F.2d 897, 899 (Fed. Cir. 1986). It is Petitioner's burden to prove that a relied upon cited reference is a printed publication. *Medtronic, Inc. v. Barry*, 891 F.3d 1368, 1380 (Fed. Cir. 2018) (citing *Blue Calypso, LLC v. Groupon, Inc.*, 815 F.3d 1331, 1350–51 (Fed. Cir. 2016)); *see also Jazz Pharms., Inc. v. Amneal Pharms., LLC*, 895 F.3d 1347, 1356 (Fed. Cir. 2018) (citation omitted) ("IPR Petitioner [] had the burden to prove that a particular reference is a printed publication.").

The Federal Circuit has explained that "public accessibility" is "the touchstone" in determining whether a reference is a printed publication. *Blue Calypso*, 815 F.3d at 1348 (quoting *Hall*, 781 F.2d at 899). "'A given reference is "'publicly accessible'" upon a satisfactory showing that such document has been disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art exercising reasonable diligence, can locate it.'" *SRI Int'l, Inc. v. Internet Sec. Sys., Inc.*, 511 F.3d 1186, 1194 (Fed. Cir. 2008) (quoting *Bruckelmyer v. Ground Heaters, Inc.*, 445 F.3d 1374, 1378 (Fed. Cir. 2006)).

In the Petition, Petitioner asserts that the Concert Backgrounder is prior art under at least pre-AIA 35 U.S.C. § 102(b) because it was "publically accessible by at least January 27, 2009, as shown in the cached WebCite®

page (Ex. 1016)[8]." Pet 27. Petitioner asserts that the cached WebCite® page was "readily accessible to the public as indicated by the WebCite® description of its services." *Id*. at 27–28. As further evidence that the Concert Backgrounder was publicly accessible via the cached WebCite®, Petitioner also relies on Exhibit 1018,[9] a law review article published in 2009 that includes the same WebCite® page in the citation for the Concert Backgrounder. *Id*. at 28. Additionally, Petitioner asserts that the Concert Backgrounder was cited in an International Search Report for a Concert PCT application. *Id*.; Ex. 1021.[10] According to the International Search Report, the WebCite® Concert Backgrounder page was accessed on May 12, 2011. Ex. 1021, 3. In the Institution Decision, the Board made a preliminary determination that Petitioner's evidence provided a sufficient showing, at that stage in the proceeding, regarding the public accessibility of the Concert Backgrounder. Inst. Dec. 17.

In the Patent Owner Response, Patent Owner asserts that Petitioner has failed to meet its burden by relying "on a 'cached WebCite® page' to demonstrate public accessibility," because "availability on the internet alone is not sufficient to show public accessibility." PO Resp. 41. Patent Owner asserts that Petitioner has not provided "evidence that WebCite® was catalogued or indexed such that POSAs would have been able to access the Concert Backgrounder on WebCite®, whether through search engine results or by a search of WebCite® itself." *Id*. at 43. Patent Owner asserts that

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[8] WebCite®, page http://www.webcitation.org/5e81SGCnl (Ex. 1016).
[9] Kristen C. Buteau, *Deuterated Drugs: Unexpectedly Nonobvious?*, J. HIGH TECH. LAW 22–74 (2009) (Ex. 1018).
[10] International Search Report PCT/US2011/025472, published August 21, 2011 (Ex. 1021).

Petitioner's evidence establishes only that the Concert Backgrounder was available on WebCite® in 2009, and that the author of the law review article and the examiner who completed the International Search Report both "possessed the full WebCite address for the Concert Backgrounder." *Id*. at 44–45.

In response to the discovery requests that we authorized Petitioner to serve on Patent Owner relating to the Concert Backgrounder, Paper 54, Patent Owner admits that the Concert Backgrounder is "a true and correct copy of a document prepared by, or on behalf of, Patent Owner," but asserts that it does not have sufficient information to admit or deny (1) whether that document was prepared in 2007, (2) that the 2007 copyright date on the document is accurate, or (3) that the document was distributed to business partners between 2007 and 2009. Ex. 1139, 3–5. Patent Owner, however, acknowledges that it submitted an Information Disclosure Statement, dated November 7, 2011, which listed the Concert Backgrounder with a 2007 date, and "retrieved from the Internet: URL: http//www.webcitation.org/5e81SGCnl." *Id*. at 6. According to Patent Owner, that action "reflects Concert's practice of submitting to the Patent Office documents cited by an examiner in a European Search Report of a counterpart application." *Id*.

Thus, Petitioner has provided evidence that the specific webcitation.org website containing the Concert Backgrounder was disseminated and accessible to at least patent examiners and an author of a law review article before the critical date because those individuals interested in the art possessed the precise website URL that functioned as a link to the reference. Further, the evidence allows us to infer that Concert

Backgrounder was viewed or downloaded by those individuals before the critical date, as they referenced it in their own published documents. Those factors overcome the absence of evidence demonstrating that the website containing the article was indexed or catalogued in a manner that was findable by an internet search engine. As a result, we find Petitioner has demonstrated that the Concert Backgrounder was "'sufficiently accessible to the public interested in the art'" so as to allow a determination that the reference is a printed publication. *Blue Calypso*, 815 F.3d at 1348 (quoting *In re Cronyn*, 880 F.2d 1158, 1160 (Fed. Cir. 1989).

Moreover, as the Federal Circuit has explained, "the presence of a 'research aid' can also establish public accessibility." *Id*. at 1350 (citing *Bruckelmyer*, 445 F.3d at 1379). In the Reply, Petitioner asserts that the same link to access the document that was disseminated to and accessed by the patent examiners and law review article author was subsequently published by those individuals, before the critical date, in a search report, an Information Disclosure Sheet, and a law review article directed to deuterated drugs, allowing others interested and ordinarily skilled in the subject matter exercising reasonable diligence to similarly access the document using the same webcitation.org website. Pet. Reply 62, 23–26.

We have considered Patent Owner's arguments challenging the sufficiency of Petitioner's evidence, *see* PO Sur-Reply 2–4, however, it is apparent that the published items containing the webcitation.org URL would have provided a skilled artisan with a sufficient roadmap to the Concert Backgrounder. *See Blue Calypso*, 815 F.3d at 1350 ("An adequate roadmap . . . should at least provide enough details from which we can determine that an interested party is reasonably certain to arrive at the destination: the

potentially invalidating reference."). Indeed, the Federal Circuit has recognized that "a published article with an express citation to the potentially invalidating reference would similarly provide the necessary guidance." *Id.* Such is the case here.

Accordingly, based on the facts in this case, we determine that Petitioner's evidence demonstrating publication of the Concert Backgrounder on the internet, along with the dissemination of the website to patent examiners and an author of a law review article directed to the subject matter of the reference, provides "a satisfactory showing that such document has been disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art exercising reasonable diligence, can locate it." *SRI Int'l*, 511 F.3d at 1194 (quotation marks and citation omitted).

Moreover, based upon the record as a whole, we find that Petitioner's evidence demonstrates that the patent documents and law review article published by those individuals function as "research aids" because they included as an express citation to the Concert Backgrounder a link to its location on the internet. Thus, we conclude that Petitioner has met its burden of demonstrating that the Concert Backgrounder was publicly accessible prior to the critical date so as to render it a "printed publication" under § 102(b). As a result, we recognize the Concert Backgrounder as prior art.

5. Obviousness Analysis

A patent claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the claimed subject matter and the prior art are such that the subject matter, as a whole, would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which the subject matter pertains. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations, including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of skill in the art; and (4) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

We generally follow a two-part inquiry to determine whether a new chemical compound would have been obvious over particular prior art compounds. *Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1291–93 (Fed. Cir. 2012). First, we determine "whether a chemist of ordinary skill would have selected the asserted prior art compounds as lead compounds, or starting points, for further development efforts." *Id.* at 1291. Second, we analyze whether there was a reason to modify a lead compound to make the claimed compound with a reasonable expectation of success. *Id.* at 1292.

(a) Lead Compound

A lead compound is defined as "'a compound in the prior art that would be most promising to modify in order to improve upon its . . . activity and obtain a compound with better activity.'" *Otsuka*, 678 F.3d at 1291 (quoting *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357 (Fed. Cir. 2007)). Stated another way, "a lead compound is '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)). Importantly, the analysis of whether a person of ordinary skill in the art would have chosen the prior art compound as a lead compound "is guided by evidence of the compound's pertinent properties," including "positive

attributes such as activity and potency," "adverse effects such as toxicity," and "other relevant characteristics in evidence." *Id.* at 1292 (citations omitted).

Based on our review of the record as a whole, we determine that the preponderance of the evidence supports finding that a person of ordinary skill in the art would have chosen ruxolitinib as a lead compound. It is "the possession of promising useful properties in a lead compound that motivates a chemist to make structurally similar compounds." *Otsuka*, 678 F.3d at 1292–93 (quotation marks and citation omitted). As Petitioner notes, Rodgers expressly claims ruxolitinib and its isomers. Pet. 50; Ex. 1007, claims 1–3. Moreover, Shilling states that ruxolitinib is "a potent, selective inhibitor of Janus tyrosine kinase1/2 and the first investigational drug of its class in phase III studies for the treatment of myelofibrosis." Ex. 1005, Abstract.

Thus, we find that the Rodgers and Shilling demonstrate "useful properties" of ruxolitinib that would have led a person of ordinary skill in the art to choose ruxolitinib as a lead compound to make structurally similar compounds. *See Otsuka*, 678 F.3d at 1292–93. Patent Owner does not argue otherwise. Rather, Patent Owner asserts that there would have been a lack of motivation to modify ruxolitinib in the manner proposed by Petitioner, i.e., deuteration, and no reasonable expectation of success in doing so. PO Resp. 46–66. We address those arguments, in turn, below.

(b) Reason to Make the Claimed Compounds/Composition

Petitioner asserts that Rodgers discloses the compound and isomer that is ruxolitinib and teaches that the compounds of its invention include those in which hydrogen is replaced with deuterium isotopes. Pet. 50 (citing

Ex. 1007, 3[2]:13–17, Claims 1–3; Ex. 1002 ¶¶ 130, 133). According to Petitioner and its declarant, Dr. Guengerich, the "octa-deuterated" and "tetra-deuterated" ruxolitinib analogs recited in the challenged claims, *see* Pet. 25 (asserting which challenged claims read on the octa-deuterated or tetra-deuterated ruxolitinib analogs), differ only by the deuteration of the cyclopentyl ring (i.e., different isotopes of the same atom). Pet. 30 (citing Ex. 1002 ¶ 33). Petitioner asserts that a person of ordinary skill in the art would have been motivated to modify Rodgers's ruxolitinib compounds to yield the claimed subject matter based upon the teachings of Shilling and the Concert Backgrounder. *Id*. at 51.

In particular, Petitioner asserts that Shilling teaches that oxidative metabolism occurs almost entirely on the cyclopentyl ring of ruxolitinib at Y^2 and Y^3. Pet. 50–51 (citing Ex. 1002 ¶¶ 130–134; Ex. 1007, 3:13–17; Ex. 1005). Petitioner asserts that the Concert Backgrounder explains that "deuterium substitution has the potential to create new chemical entities with improved safety, tolerability, and efficacy" and that deuterium compounds useful for this technique are "based on drugs with known efficacy and safety that address clinically validated targets." *Id*. at 51–52 (citing Ex. 1006, 2; Ex. 1002 ¶¶ 71–73, 136). According to Dr. Guengerich, the Concert Backgrounder also teaches that compounds should be selected that have known "metabolic 'hot spots'" and should be deuterated at some or all of these metabolic hot spots. Ex. 1002 ¶ 136. Therefore, according to Petitioner, a person of ordinary skill in the art "would have been motivated to apply the techniques disclosed in the Concert Backgrounder to ruxolitinib and/or the deuterated ruxolitinib of Rodgers because ruxolitinib was a claimed compound of the invention in Rodgers and ruxolitinib contained

well-identified sites of oxidative metabolism in *in vivo* metabolism, as shown in Shilling." Pet. 54 (citing Ex. 1002 ¶¶ 135–136). Additionally, Petitioner asserts that Shilling and the Concert Backgrounder provide a motivation to make the recited tetra- and octa-deuterated ruxolitinib analogs and compositions because those references suggest that such analogs may display superior ADME properties. *Id*. at 31.

Further, Petitioner asserts that the motivation is supplied by the fact that the "claimed and prior art compounds possess a 'sufficiently close relationship . . . to create an expectation,' in light of the totality of the prior art, that the new compound will have 'similar properties' to the old." Pet. 30 (quoting *Aventis Pharma Deutschland GmbH v. Lupin Ltd*., 499 F.3d 1293, 1301 (Fed. Cir. 2007) (citing *In re Dillon*, 919 F.2d 688, 692 (Fed. Cir. 1990)). According to Petitioner, a person of ordinary skill in the art would have known that "deuterium-substituted compounds retain their . . . selectivity and potency comparable to their hydrogen analogs." *Id*. (citing Ex. 1002 ¶ 55); Ex. 1013,[11] 5 ("At Concert, 'we've never seen any biologically relevant differences in target selectivity or potency of a drug when we deuterated it.'").

Based upon our review of the record as a whole, we find that the preponderance of the evidence supports Petitioner's assertion that the combined teachings of Rodgers, Shilling, and the Concert Backgrounder would have provided a person of ordinary skill in the art a reason to deuterate Rodgers's ruxolitinib compounds at their metabolic "hot spots," as identified by Shilling, in the manner taught by the Concert Backgrounder to

[11] A. Yarnell, *Heavy-Hydrogen Drugs Turn Heads Again*, 87 CHEM. ENG'G NEWS 36–39 (2009) (Ex. 1013).

achieve the potential benefits that the Concert Backgrounder disclosed, e.g., improved safety, tolerability, and efficacy. We also determine that the preponderance of the evidence supports Petitioner's assertion that a motivation to make deuterated ruxolitinib compounds and compositions exists based upon the structural similarity between those claimed compounds and the prior art compounds, as evidenced by the testimony of Dr. Guengerich, Ex. 1002 ¶ 55, and the remarks by a Concert representative in an article published in the Chemical & Engineering News journal, Ex. 1013, 39. In reaching those determinations, we considered Patent Owner's arguments and found them deficient as explained in the following discussion.

Patent Owner asserts that a person of ordinary skill in the art would not have been motivated to modify ruxolitinib through deuteration because "the prior art taught that ruxolitinib had dose-limiting toxic side effects that could be exacerbated by slowing its metabolism" with a deuterium substitution. PO Resp. 47. In support of this argument, Patent Owner relies upon the similarly-stated testimony of its declarant, Dr. Ortiz de Montellano, *see id*. at 48 (citing Ex. 2057 ¶ 41), and upon cases wherein either "evidence that the chemical modification of [prior art compound] would have been unattractive to a person of ordinary skill for fear of disturbing the chemical properties whereby [the compound] function[ed] effectively," *Millennium Pharms. Inc. v. Sandoz Inc.*, 862 F.3d 1356, 1366 (Fed. Cir. 2017), or "the prior art's teachings undermine the very reason being proffered as to why a person of ordinary skill would have combined the known elements," *DePuy Spine v. Medtronic Sofamor Danek Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009). PO Resp. 48. According to Patent Owner, those cases apply here

because "ruxolitinib's dose-dependent toxicity would have dissuaded POSAs from trying to change the metabolic profile via deuteration." *Id*.

Although a person of ordinary skill in the art may have known that ruxolitinib exhibits dose-dependent side effects, Patent Owner and Dr. Ortiz de Montellano have not provided evidence that deuterating Rodgers's compounds would have been "unattractive to a person of ordinary skill for fear of disturbing the chemical properties" of those compounds, or that the skilled artisan would have found doing so would "undermine" the purpose of modifying such compounds, as in the cited cases. Nor have Patent Owner and Dr. Ortiz de Montellano offered other evidence that supports avoiding deuterating the drug based upon known dose-dependent side effects of ruxolitinib. *See* PO Resp. 47–48; Ex. 2057 ¶ 41.

For example, Patent Owner asserts that thrombocytopenia is a dose-dependent side effect of ruxolitinib. PO Resp. 10–11, 47. The journal article relied upon by Patent Owner teaches that such "events rarely led to treatment discontinuation . . . and were generally manageable with dose modifications, transfusions of packed red cells, or both." Ex. 2054, 795. In other words, as the side effect is dependent upon dose, the side effect may be managed by a dose adjustment.

Dr. Ortiz de Montellano acknowledged that teaching when he stated that hematological side effects of ruxolitinib "were known to be dose-dependent, as evidenced by recommendations to lower the dose of ruxolitinib if they occurred." Ex. 2057 ¶ 41 (citing Ex. 2054). Additionally, at his deposition, he responded affirmatively when asked "if you affect first-pass metabolism by deuteration, you can lower the dose of the deuterated drug to get the same area under the curve as the undeuterated drug?" Ex.

1088, 66:8–15. In other words, the dose of a deuterated drug may be lowered to achieve the same concentration as the undeuterated drug. In view of those acknowledgments, it is peculiar that Dr. Ortiz de Montellano's declaration testimony does not address whether a person of ordinary skill in the art would have managed side effects of deuterated ruxolitinib in the same manner. Without such consideration, we assign little weight to his conclusion that a person of ordinary skill in the art would have lacked motivation to deuterate ruxolitinib based upon known dose-dependent side effects of the undeuterated drug.

Patent Owner also asserts that, because "[d]euteration is relatively expensive and highly unpredictable," a person of ordinary skill in the art "would have pursued other clinically-validated strategies for increasing a drug's metabolic stability . . . such as the use of extended release dosage forms." PO Resp. 49 (citing Ex. 2057 ¶¶ 39, 43). According to Patent Owner, Petitioner has not shown "why POSAs would have been motivated to modify ruxolitinib's metabolism by deuteration, rather than other available methods for modifying metabolic profile." *Id*. Further, Patent Owner asserts that "the Petition merely sets forth some general reasons why POSAs might have been motivated to deuterate drugs generally, but provides no justification for why POSAs would have been motivated to deuterate ruxolitinib in particular to arrive at the claimed compounds." *Id*. at 49–50.

Insofar as Patent Owner argues that motivation to modify ruxolitinib with deuteration requires Petitioner to establish that a person of ordinary skill in the art would not have instead been motivated to modify the metabolic profile of ruxolitinib by using "other available methods" for doing

so, e.g., "use of extended release dosage forms," PO Resp. 49, we disagree. If that argument is intended to suggest that some prior art disclosing "other available methods" teaches away from the claimed invention, the argument fails as Patent Owner has not shown anything in the prior art describing such alternatives and criticizing, discrediting, or otherwise discouraging deuteration. *See In re Fulton*, 391 F.3d 1195, 1201 (Fed. Cir. 2004).

Further, we disagree with Patent Owner's assertion that Petitioner "provides no justification for why POSAs would have been motivated to deuterate ruxolitinib in particular to arrive at the claimed compounds." PO Resp. 49–50. As discussed above, Petitioner has shown persuasively how a person of ordinary skill in the art would have understood from Shilling that Rodgers's ruxolitinib compounds feature the metabolic "hot spots" targeted by the Concert Backgrounder for deuteration, and that the Concert Backgrounder teaches that such deuteration has the potential to improve the safety, tolerability, and efficacy of those compounds. *See* Pet. 31, 50–54.

Patent Owner asserts also that Petitioner's asserted motivation to modify ruxolitinib based upon structural similarities between the prior art compounds and the claimed compounds is deficient because Petitioner has not shown that "POSAs would have had 'an expectation,' in light of the totality of the prior art, that the new compound will have 'similar properties' to the old." PO Resp. 52 (citing *Aventis*, 499 F.3d at 1301 (quoting *Dillon*, 919 F.2d at 692)). Patent Owner asserts that such similar properties cannot be assumed based upon similar structures. *Id*. at 54 (citing *Anacor Pharm., Inc. v. Iancu*, 889 F.3d 1372, 1385 (Fed. Cir. 2018) ("[T]he chemical arts are unpredictable and that similar structures do not always result in similar properties.")). Patent Owner asserts that Dr. Guengerich's reliance on the

Concert Backgrounder is insufficient, as that reference only suggests that deuterated drugs have not exhibited "any biologically relevant differences in target selectivity or potency" from the starting drugs. *Id*. at 56. According to Patent Owner, Dr. Guengerich "does not even assert that POSAs would have expected that *all* the relevant properties would be similar," i.e., pharmacokinetic and ADME properties as well. *Id*.

Petitioner asserts that it has provided sufficient evidence for a person of ordinary skill in the art to expect that deuterated ruxolitinib and Rodgers's ruxolitinib have similar properties. Pet. Reply 12–13. Based on the record as a whole, we agree with Petitioner. Petitioner's declarant, Dr. Guengerich, explains that "deuterium and hydrogen are very similar in size and electronic properties. Thus, deuterium-substituted compounds retain their molecular shape and their basic electronic properties, and therefore, have selectivity and potency comparable to their hydrogen analogs." Ex. 1002 ¶ 55. We find his explanation persuasive as it is based in chemistry and supported by the Concert Backgrounder. Further, we find that such testimony is sufficient to provide a skilled artisan with an expectation that the claimed and prior art compounds would have similar properties, in general. Petitioner further supports its position that those compared compounds would have been expected to have similar properties with the deposition testimony of Patent Owner's declarant, Dr. Harbeson, who explained that at Concert, "our experience has been that replacement of hydrogen with deuterium does not change the intrinsic biologic activity or pharmacology of the molecule. And therefore any deuterated analog of ruxolitinib we would presume to retain the same intrinsic biology and pharmacology." Ex. 1089, 97:4–18.

(c) Reasonable Expectation of Success

According to Petitioner and Dr. Guengerich, synthesizing the claimed octa- and tetra-deuterated ruxolitinib analogs from the known ruxolitinib compounds was well within the skill in the art at the time of the invention. Pet. 32–33 (citing Ex. 1002 ¶¶ 104–105). Additionally, Petitioner asserts that the skilled artisan would have expected those analogs to perform at least as well as ruxolitinib. *Id*. at 33 (citing Ex. 1002 ¶¶ 91–93, 104–105). In addition to Dr. Guengerich's testimony, Petitioner draws support for that assertion from the comments of a Concert representative in a published journal article explaining that he and his colleagues had "never seen any biologically relevant differences in target selectivity or potency of a drug when [they] deuterated it." *Id*. (quoting Ex. 1013, 5).

Petitioner and Dr. Guengerich further contend that an ordinarily skilled artisan would have expected improved metabolic stability over ruxolitinib based on Shilling and Concert Backgrounder. Pet. 33–39; Ex. 1002 ¶¶ 94–108. Petitioner asserts that Shilling's teaching that ruxolitinib metabolism is largely restricted to the cyclopentyl ring would have suggested to a skilled artisan that the compound was an ideal candidate for the deuteration disclosed by the Concert Backgrounder. *Id*. at 34 (citing Ex. 1002 ¶¶ 83–84).

In particular, Concert Backgrounder discloses an example of deuteration with the drug torcetrapib, wherein six of the twelve analogs demonstrated improved metabolic stability. Ex. 1002 ¶¶ 74–77. According to Dr. Guengerich, a person of ordinary skill in the art would have expected those six analogs to show enhanced metabolic stability based on known metabolic pathways of torcetrapib. *Id*. Dr. Guengerich explains that each

metabolite of torcetrapib is metabolized at least at one known position of the compound's structure. *Id*. When that position or "hotspot" is fully deuterated, metabolism is predictably altered. *Id*. ¶ 77. Thus, Dr. Guengerich considers the deuteration strategy disclosed in the Concert Backgrounder to be somewhat predictable. *Id*.

Moreover, Dr. Guengerich explains that a reasonable expectation of success would have been implicitly recognized by a person of ordinary skill in the art by the Concert Backgrounder's statement that deuteration "substantially reduced R&D [research and development] risk, time, and expense," which is due to the "relative ease and predictability of producing deuterated analogs of known pharmacologically-active compounds and suggests to a POSA a reasonable expectation of success." *Id*. ¶ 73.

Patent Owner asserts that Petitioner has not established that a person of ordinary skill in the art would have had a reasonable expectation of successfully making the claimed invention. PO Resp. 57–67. Patent Owner bases that contention not on whether a person of ordinary skill in the art could have reasonably expected to successfully synthesize the claimed octa- and tetra-deuterated ruxolitinib analogs from known ruxolitinib compounds. Indeed, Patent Owner does not contend that such a structural modification would not have been within the skill in the art and routine. Nor does Patent Owner assert that such analogs would not have been expected to remain effective in modulating the activity of Janus kinases or treating diseases related to activity of those kinases, as Rodgers discloses for undeuterated ruxolitinib. *See* PO Resp. 20–23, 66–67 and PO Sur-Reply 12–13 (addressing potential variable pharmacokinetic changes in deuterated ruxolitinib, i.e., potential dosage considerations).

Rather, Patent Owner bases its contention on assertions that a person of ordinary skill in the art would have had no reasonable expectation of achieving either an *in vitro* or *in vivo* kinetic isotope effect (KIE), i.e., metabolic change from deuterating ruxolitinib, PO Resp. 58–66, and would not have been able to predict *a priori* the effect of deuteration on the clinical profile (e.g., half-life) of the drug, *id*. at 66–67. However, as Petitioner correctly asserts, the challenged claims do not recite any of those features. Pet. Reply 15.

A reasonable expectation of success inquiry involves considering whether a person of ordinary skill in the art would have had a reasonable expectation of successfully making the *claimed invention* in light of the prior art. *See Amgen, Inc. v. F. Hoffman–La Roche Ltd.*, 580 F.3d 1340, 1362 (Fed. Cir. 2009) ("An obviousness determination requires that a skilled artisan would have perceived a reasonable expectation of success in making the invention in light of the prior art.") (citing *In re Kubin*, 561 F.3d 1351, 1360 (Fed. Cir. 2009) ("[S]tated in the familiar terms of this court's longstanding case law, the record shows that a skilled artisan would have had a resoundingly 'reasonable expectation of success' in deriving the claimed invention in light of the teachings of the prior art.")).

Based upon our review of the record as a whole, we find that the preponderance of the evidence supports Petitioner's assertion that the combined teachings of Rodgers, Shilling, and the Concert Backgrounder would have provided a person of ordinary skill in the art a reasonable expectation of successfully deuterating Rodgers's ruxolitinib compounds at their metabolic "hot spots," as identified by Shilling, and in the manner taught by the Concert Backgrounder. Insofar as Petitioner's motivation to

do so involved an "expectation that these ruxolitinib analogs *may display* superior ADME properties as compared to non-deuterated ruxolitinib," Pet. 31 (emphasis added), we further find that Petitioner has established by a preponderance of the evidence that a skilled artisan would have had a reasonable expectation that the synthesized ruxolitinib analogs "may display" superior ADME properties, based upon the combined teachings of Shilling and the Concert Backgrounder, as explained above in our discussion of a motivation to combine. Patent Owner's arguments to the contrary attempt to avoid obviousness "by a showing of some degree of unpredictability in the art" despite the reasonable probability of success supplied by the structural similarity between the compounds and the motivation provided by the cited prior art that would have led a skilled artisan to modify known ruxolitinib compounds in the manner disclosed by the Concert Backgrounder. *See Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007) ("[C]ase law is clear that obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success. . . . [T]he expectation of success need only be reasonable, not absolute." (citations omitted)).

Based on the foregoing, we agree with Petitioner that one of ordinary skill in the art would have had a reason to deuterate Rodgers's ruxolitinib compounds, given the combined teachings of Rodgers, Shilling, and the Concert Backgrounder, and that those teachings would have provided a reasonable expectation that doing so would successfully yield the inventions of claims 1–15 of the '149 patent.

Our analysis continues with a discussion of Patent Owner's asserted secondary considerations of nonobviousness. *Transocean Offshore Deepwater Drilling, Inc. v. Maersk Drilling USA, Inc.*, 699 F.3d 1340, 1349 (Fed. Cir. 2012).

(d) Secondary Considerations

Patent Owner asserts that the claimed invention yields unexpected results and satisfies a long-felt need. PO Resp. 67.

(i) Unexpected Results

According to the Federal Circuit, "[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 Co. v. Teva Pharms. USA, Inc.*, 752 F.3d 967, 977 (Fed. Cir. 2014).

Patent Owner asserts that one specific deuterated ruxolitinib compound disclosed by the '149 patent, CTP-543,[12] exhibits "two important and clinically meaningful unexpected advantages." PO Resp. 68. First, Patent Owner asserts that CTP-543 provides an "increased time in the therapeutic window," when compared to prior art ruxolitinib. *Id*. More specifically, Patent Owner states that CTP-543 "has the potential to demonstrate an unexpected clinical benefit by maintaining safe and effective drug levels for a longer period." *Id*. Second, Patent Owner asserts that CTP-543 provides an "increased clinical response at a given dose," when

[12] The parties refer to Compound 111 disclosed in the '149 patent, Ex. 1001, 37:28–40, as "Compound 111," "CTP-543," and "octa-deuterated ruxolitinib," interchangeably.

compared to prior art ruxolitinib. *Id*. In particular, Patent Owner asserts that "individuals in Concert's Phase I study with the shortest ruxolitinib $t_{1/2}$ values unexpectedly had the greatest improvement in $t_{1/2}$ values when given CTP-543." *Id*. at 69.

Petitioner asserts that Patent Owner's secondary indicia of nonobviousness are not commensurate in scope with the challenged claims. Pet. Reply 2–3. Petitioner asserts also that Patent Owner's results relating to the "therapeutic window" for CTP-543 and its increased half-life for fast metabolizers would have been expected. *Id*. at 8–12. Additionally, Petitioner asserts that Patent Owner relies upon results demonstrating, at best, "an insignificant difference in degree." *Id*. at 7–8.

As the Federal Circuit has explained, "[u]nexpected results that are probative of nonobviousness are those that are 'different in kind and not merely in degree from the results of the prior art.'" *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 739 (Fed. Cir. 2013) (quoting *Iron Grip Barbell Co. v. USA Sports, Inc.*, 392 F.3d 1317, 1322 (Fed. Cir. 2004)).

Having reviewed the arguments and the evidence, we find that Patent Owner's asserted evidence of unexpected results demonstrates, at most, results that differ in degree over the results observed with the closest prior art, rather than in kind. Patent Owner plainly refers to the results as demonstrating an "*increased time* in the therapeutic window," and an "*increased clinical response* at a given dose," when compared to the closest prior art. PO Resp. 68 (emphasis added). Indeed, when describing the increased clinical response, Patent Owner asserts, "[w]here there is an observed KIE, the expectation is that there would be the same relative (percentage) increase in half-life for all metabolizers. . . . However, Concert

unexpectedly found that CTP-543 provides a *greater relative (percentage) increase in half-life* for more rapid ruxolitinib metabolizers." Paper 85, 15 (emphasis added). Even if commensurate in scope and taken as true and unexpected, Patent Owner's asserted results for CTP-543 demonstrate an increase in the same clinical activity observed with ruxolitinib, and therefore represent merely a difference in degree and not in kind. *See Galderma Labs., L.P.*, 737 F.3d at 739 (citing "*In re Harris*, 409 F.3d 1339, 1344 (Fed. Cir. 2005) (finding increased efficacy, measured by percentages, to be a difference of degree and not of kind)"). Accordingly, the results asserted to demonstrate an "increased time in the therapeutic window" and an "increased clinical response at a given dose" for CTP-543 as compared to ruxolitinib are not of a "kind" so as to support a finding of nonobviousness of the challenged claims.

(ii) Long-Felt Need

Patent Owner asserts that "[t]here has been a long-felt need for an AA [alopecia areata] treatment that is not only effective, but also safe for prolonged use." PO Resp. 70. According to Patent Owner, "existing treatment options for AA patients in 2012 promised little efficacy and carried potentially significant side effects." *Id*. In particular, Patent Owner recognizes that the prior art ruxolitinib "may have potential use in moderating AA," however, the side effects of that drug include a risk of anemia and thrombocytopenia. *Id*. Patent Owner asserts that "Concert is developing CTP-543 as a first-in-class treatment satisfying the long-felt need for a safe and effective AA treatment." *Id*. Patent Owner submits that CTP-543 is "uniquely suited to meet this need" because deuteration confers a longer half-life and a longer time in the therapeutic window than ruxolitinib.

Id. at 71. According to Patent Owner and its declarant, Dr. Mackay-Wiggan, "[t]his increased time in the therapeutic window and potential for greater therapeutic response at a given dose show the promise of CTP-543 to help AA patients while mitigating the risk of undesirable side effects posed by ruxolitinib." *Id*. (citing Ex. 2048 ¶ 38). Additionally, Patent Owner asserts that "[t]he FDA's award of a 'Fast Track' designation to CTP-543 underscores the importance of the need satisfied by the octa-deuterated compound of the '149 patent." *Id*.

Petitioner asserts that Concert has not met the alleged long-felt need because, among other reasons, "CTP-543 is not 'FDA-approved' for anything, let alone AA." Pet. Reply 3.

Based upon our consideration of the arguments and the evidence, we find that Patent Owner's assertion that CTP-543 *has satisfied* a long-felt but unmet need for treating alopecia areata is unsupported. The pronouncement is premature. Indeed, Patent Owner and Dr. Mackay-Wiggan admit as much. Patent Owner describes meeting such long-felt need in terms of CTP-543 providing a "potential" treatment of AA with a lower dose and fewer side effects. PO Resp. 71. Similarly, Dr. Mackay-Wiggan describes Concert's data as "promising regarding the *potential* use of CTP-543 for the treatment of alopecia areata." Ex. 2048 ¶ 38 (emphasis added). At the oral hearing, counsel for Patent Owner candidly agreed that the contention is based upon the "likely efficacy" of CTP-543 to meet a need for treating AA from modeling performed, and that the FDA award of a Fast Track designation to CTP-543 indicates a "likelihood" that CTP-543 "will fulfill the long-felt need and meet the secondary consideration." Tr. 57:17–58:7.

Accordingly, we find that the evidence submitted relating to the "potential" or "likelihood" of CTP-543 treating alopecia areata does not demonstrate that it satisfies a long-felt unmet need so as to support a finding of nonobviousness of the challenged claims.

(e) *Conclusion as to Obviousness*

We base our final determination regarding obviousness upon an analysis of the foregoing arguments and evidence. In particular, we have considered the secondary considerations of nonobviousness and accorded them appropriate weight along with all of the *Graham* factors. *WBIP, LLC v. Kohler Co.*, 829 F. 3d 1317, 1328 (Fed. Cir. 2016). Accordingly, based upon the preponderance of the evidence, we conclude that the challenged claims are unpatentable as obvious over Rodgers, Shilling, and the Concert Backgrounder.

D. Remaining Ground of Obviousness

In the remaining ground of obviousness, Petitioner asserts that claims 1–15 are unpatentable over the combination of the Jakafi Label, Shilling, and the Concert Backgrounder. Pet. 26–43. Because Petitioner challenges the same claims in this ground as we just concluded were unpatentable over a similar combination of references and based upon a similar rationale as relied upon here, we decline to reach this ground.

III. PETITIONER'S MOTION TO EXCLUDE

Petitioner moves to exclude, in whole or in part, Exhibits 2001, 2002, 2019, 2048, 2057, 2071, 2078, 2079, 2099–2101, 2103, 2104, 2112, 2122, and 2123. Paper 94 ("Exclude Mot."). Patent Owner opposes the motion. Paper 102 ("Exclude Opp."). As the moving party, Petitioner has the burden

of proof to establish that it is entitled to the requested relief. 37 C.F.R. § 42.20(c).

A. Exhibits 2001, 2002, 2019, 2048, 2057, 2071, and 2079

Exhibit 2019 is referred to by Patent Owner as "Appendices to Declaration of Scott L. Harbeson, Ph.D (Exhibit 2001)." Ex. 2019, 1. Petitioner asserts that portions of Appendices 3 and 4 of Exhibit 2019 were relied upon in the declaration testimony of Patent Owner's declarants, Dr. Harbeson (Exhibits 2001, 2071, and 2079), Dr. Baille (Ex. 2002), Dr. Mackay-Wiggan (Exhibit 2048), and Dr. Ortiz de Montellano (Ex. 2057). Exclude Mot. 7. Petitioner contends that Appendices 3 and 4 are unauthenticated hearsay and should be excluded, along with the paragraphs in each of the above-mentioned declarations that rely upon those appendices, under Federal Rules of Evidence ("FRE") 802, 901 and 902. *Id*. at 1–9.

Patent Owner asserts that Petitioner's motion should be denied because "Petitioner failed to 'identify the grounds for the objection with sufficient particularity to allow correction in the form of supplemental evidence.'" Exclude Opp. 2 (quoting 37 C.F.R. § 42.64(b)(1)). According to Patent Owner, Petitioner's Objections were directed to Exhibit 2019, as a whole, which represents seven appendices, whereas its motion is directed to only two of those appendices. *Id*.

Petitioner responds by noting that its objections specifically raise the bases for its motion to exclude. Paper 103, 2. We agree with Petitioner that its objections to Exhibits 2001, 2002, 2019, 2048, 2057, 2071, and 2079 complied with 37 C.F.R. § 42.64(b)(1). For example, the objections challenged Exhibit 2019 by asserting that it (a) lacks authentication under

FRE 901 and is not self-authenticating as the source of the exhibit, date of its creation, and author(s) are unidentified; (b) represents hearsay under FRE 802 by offering out of court statements of the unidentified author(s) for the truth of the matters asserted "(e.g., that certain experiments were conducted and generated certain results)," as hearsay within hearsay. Paper 18, 4. Further, in the objections of 2001, 2002, 2048, 2057, 2071, and 2079, Petitioner refers to the objection to Exhibit 2019 and sets forth the paragraphs of each challenged exhibit that it seeks to exclude based upon asserted reliance on Exhibit 2019 therein. *See* Paper 18, 1–3; Paper 32, 3–4. Moreover, we agree with Petitioner that the fact that its motion seeks to preserve its objections to those exhibits with regard to only a portion of Exhibit 2019, i.e., Appendices 3 and 4, does not render the objections encompassing those items insufficient, as they too were set forth with "sufficient particularity," as required.

Substantively, Patent Owner asserts that Dr. Harbeson's testimony regarding the source and content of the data in Appendices 3 and 4 is sufficient to authenticate those portions of Exhibit 2019. Exclude Opp. 3–4. Patent Owner characterizes Appendices 3 and 4 as a "summary" of pharmacokinetic data "excerpted from Concert's clinical study reports" relating to CTP-543 and relied upon by Dr. Harbeson in formulating his opinions. *Id*. at 6 n.2. According to Patent Owner, Dr. Harbeson demonstrated his familiarity with the study design, subjects, timing, dosages, sampling, and data acquisition and analysis. *Id*. at 4 (citing Ex. 2001 ¶¶ 2, 11–16). Regarding hearsay, Patent Owner asserts that Appendices 3 and 4 "reflect records of a regularly conducted activity and not hearsay." *Id*. at 7.

Patent Owner contends that if Appendices 3 and 4 are found to be unauthenticated hearsay, "the data and methodology presented in Exhibit 2019 is the sort that an expert would rely on, and as such, Exhibits 2001, 2002, 2048, and 2057 should not be excluded." *Id*. at 10.

Based upon our review of the arguments and evidence, we note that Petitioner demonstrates a strong case for finding that Appendices 3 and 4 of Exhibit 2019 have not been authenticated and likely contain hearsay. *See* Exclude Mot. 1–9 and Paper 103, 1–3. However, we decline to exclude that material. As we recognized in *Argentum Pharmaceuticals LLC v. Research Corp. Technologies, Inc*., Case IPR2016-00204, slip op. 52 (PTAB Mar. 22, 2017) (Paper 85), "under FRE 703, the proponent of an expert opinion may disclose otherwise inadmissible evidence underling 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 this case, we conclude that our ability (and that of the declarant(s) for Petitioner) to evaluate the summary and methodology set forth in Appendices 3 and 4 that served as a basis for testimony provided by Patent Owner's declarants outweighs any prejudicial effect posed by those portions of Exhibit 2019. Indeed, when assigning weight, if any, to testimony based on Appendices 3 and 4, we may factor in the reliability of such information presented as a summary of data that was excerpted from clinical study reports.

Accordingly, we deny the Motion to Exclude with respect to Exhibits 2001, 2002, 2019, 2048, 2057, 2071, and 2079.

B. Exhibit 2078

Exhibit 2078 is a journal article titled "Effect of deuteration on metabolism and clearance of Nerispirdine (HP184) and AVE5638." Ex. 2078, 3831. Petitioner asserts that Exhibit 2078 appears to have been published in 2015, long after the 2012 priority date of the '149 patent. Exclude Mot. 9. Therefore, Petitioner asserts that the exhibit is irrelevant under FRE 401 and 402. *Id*.

Patent Owner acknowledges the post-priority date publication of Exhibit 2078 and asserts that such date "does not detract from its relevance" regarding the Patent Owner contentions regarding the unpredictability of effects of deuteration. Exclude Opp. 14. Further, Patent Owner asserts that arguments relating to the relevance of post-filing publication dates concern the weight given to that evidence and not its admissibility. *Id*. at 15.

We agree with Patent Owner that Petitioner's challenge of Exhibit 2078 is not a basis for excluding the exhibit. Rather, the post-filing publication date of a reference relied upon to indicate general knowledge of a person of ordinary skill in the art is a factor that we consider when we weigh the evidence. Further, as the Federal Circuit has explained, the Board may rely on "non-prior art evidence," in a limited capacity, i.e., in a supportive role, "e.g., indicating the level of ordinary skill in the art, what certain terms would mean to one with ordinary skill in the art, and how one with ordinary skill in the art would have understood a prior art disclosure." *Yeda Research v. Mylan Pharms. Inc.*, 906 F.3d 1031, 1041 (Fed. Cir. 2018).

Accordingly, we deny Petitioner's Motion to Exclude with respect to Exhibit 2078.

C. Exhibits 2099–2101, 2103, 2104, and 2112

Exhibits 2099–2101, 2103, 2104, and 2112 were introduced at the deposition of Dr. Shapiro and were subsequently filed. Petitioner asserts that those exhibits have not been referenced in any briefing by Patent Owner. Exclude Mot. 9. According to the Petitioner, each of those exhibits should be excluded as irrelevant under FRE 401 and 402. *Id*. at 9–10. Further, Petitioner asserts that those exhibits should be excluded as untimely and improper new evidence. *Id*. at 10.

Patent Owner states that it "does not oppose exclusion of Exhibits 2099–2101, 2103, 2104, and 2112, which are not cited in any substantive paper." Exclude Opp. 1 n.1. Accordingly, we grant Petitioner's Motion to Exclude with respect to Exhibits 2099–2101, 2103, 2104, and 2112.

D. Exhibits 2122 and 2123

Exhibits 2122 (sealed) and 2123 (public) represent the declaration of Dr. Cowden, a Concert employee, filed with Patent Owner's Reply to Petitioner's Opposition to the Contingent Motion to Amend (Paper 84). Petitioner asserts that Dr. Cowden's testimony relating to tests performed on a sample of CTP-543 obtained by Concert from a third party (Carbogen) lacks foundation under FRE 602 because "Dr. Cowden has not established personal knowledge (1) that Carbogen retained the specific CTP-543 batch, (2) that Carbogen sent to Concert a representative sample of the specific CTP-543 batch, or (3) that the sample tested at Concert was the specific CTP-543 batch in issue." Exclude Mot. 11. Petitioner asserts also that, insofar as Dr. Cowden's testimony relies on quantitative nuclear magnetic resonance ("NMR") analysis, his testimony "constitutes improper lay testimony and/or expert testimony" as he has not been shown to be an expert

in quantitative NMR. *Id*. at 11–12. Therefore, Petitioner asserts that paragraphs 6, 8–13, 15–24, and Appendix A of Exhibits 2122 and 2123 should be excluded. *Id*. at 11–14.

Patent Owner asserts that "Dr. Cowden is an expert in NMR interpretation, as it relates to drug development," and that none of his declaration testimony should be excluded as improper expert testimony. Exclude Opp. 10–11. Further, Patent Owner asserts that Dr. Cowden provided sufficient foundation for his testimony regarding his knowledge about the specific CTP-543 batch at issue. *Id*. at 14 (citing Ex. 2122 ¶ 11).

Based upon our review of the declaration testimony and briefing, it appears as though Patent Owner offers the testimony of Dr. Cowden as that of a hybrid fact witness/expert, as he provides testimony regarding the analysis of a sample batch of CTP-543 at Concert, performed under his supervision, and he provides conclusions based upon the data generated from the sample. *See, e.g.*, Ex. 2123 ¶¶ 11, 24. Dr. Cowden begins his declaration by stating that he has "personal knowledge of the facts set forth in this Declaration." *Id.* ¶ 1. He testifies also that he is employed by Concert as the "Senior Director, Chemical Development." *Id*. ¶ 2. In terms of expertise, Dr. Cowden testified that he received his Ph.D. in synthetic organic chemistry, has over 18 years of experience in the field of process chemistry, and has "routinely used nuclear magnetic resonance (NMR) to analyze organic compounds." *Id*. ¶¶ 3–4. Patent Owner refers to Dr. Cowden as an expert in NMR interpretation, and also acknowledges that his testimony is based upon personal knowledge regarding the CTP-543 sample. Exclude Opp. 10–11.

In view of those facts, we do not find that Petitioner has met its burden of demonstrating that portions of Dr. Cowden's declaration should be excluded based upon FRE 602, 701, or 702. Petitioner's objections implicate the weight and sufficiency of the testimony, rather than its admissibility. We are in a position to discern whether Dr. Cowden's testimony should be entitled to weight, either as a whole or with regard to specific issues. Further, we note that Petitioner had the opportunity to address any alleged deficiencies regarding Dr. Cowden's personal knowledge or qualifications during a deposition. As Patent Owner has explained, Dr. Cowden was offered for such an examination, however, Petitioner declined. *See* Exclude Opp. 11 n.3.

Accordingly, we deny the Motion to Exclude with respect to Exhibits 2122 and 2123.

IV. PATENT OWNER'S CONTINGENT MOTION TO AMEND

Having concluded that claims 1–15 are unpatentable under 35 U.S.C. § 103 as obvious over Rodgers, Shilling, and the Concert Backgrounder, we next consider Patent Owner's Contingent Motion to Amend the claims of the '149 patent. Proposed amended claims are set forth in the Motion. Amend Mot. 26–31 (Appendix A). Patent Owner supports its Motion with the declarations of Scott Harbeson, Ph.D. (Ex. 2001 and Ex. 2071, sealed; Ex. 2079, public), Thomas B. Baille, Ph.D., D.SC. (Ex. 2002), Julian Mackay-Wiggan, M.D., M.S. (Ex. 2048), Paul Ortiz de Montellano, Ph.D. (Ex. 2057), and Dr. Cameron Cowden, Ph.D. (Ex. 2122, sealed; Ex. 2123, public), and the original disclosure of the '149 patent (U.S. Appl. No. 14/707,912) (Ex. 2037, 1–66) ("the '912 application"), and the original disclosure of related Provisional Application No. 61/660,428 (Ex. 2073)

("the '428 application"), to which the '912 application claims priority, (collectively, the "Applications"). Amend Mot. 4.

Pursuant to *Aqua Products, Inc. v. Matal*, 872 F.3d 1290 (Fed. Cir. 2017), the Board assesses "the patentability of the proposed substitute claims without placing the burden of persuasion on the patent owner." *Id*. at 1296. The Court explained that the Patent Office may not place the burden of persuasion on a patent owner with respect to the patentability of substitute claims presented in a motion to amend. *See id*. at 1327; *see Bosch Auto. Serv. Sols. LLC v. Matal*, 878 F.3d 1027, 1040 (Fed. Cir. 2017).

As for procedural requirements regarding motions to amend, the Court stated that "the patent owner must satisfy the Board that the statutory criteria in [35 U.S.C.] § 316(d)(1)(a)–(b) and § 316(d)(3) are met and that any reasonable procedural obligations imposed by the Director are satisfied before the amendment is entered into the IPR." *Aqua Prods.*, 872 F.3d at 1305–06. In view of *Aqua Products*, the Board has issued guidance explaining,

> [A] patent owner still must meet the requirements for a motion to amend under 37 C.F.R. § 42.121 or § 42.221, as applicable. That is, a motion to amend must set forth written description support and support for the benefit of a filing date in relation to each substitute claim, and respond to grounds of unpatentability involved in the trial. Likewise, under 37 C.F.R. § 42.11, all parties have a duty of candor, which includes a patent owner's duty to disclose to the Board information that the patent owner is aware of that is material to the patentability of substitute claims, if such information is not already of record in the case.

See Memorandum "Guidance on Motions to Amend in view of *Aqua Products*" (Nov. 21, 2017) (https://www.uspto.gov/sites/default/files/documents/guidance_on_motions_to_amend_11_2017.pdf) ("Memorandum") at 2.

A. Reasonable Number of Substitute Claims

"A motion to amend may. . . propose a reasonable number of substitute claims. The presumption is that only one substitute claim would be needed to replace each challenged claim, and [that presumption] may be rebutted by a demonstration of need." 37 C.F.R. § 42.121(a)(3).

Patent Owner requests to substitute proposed claims 16–19 (the "Substitute Claims") for original claims 1, 8, 9, and 15. Amend Mot. 1. Specifically, Patent Owner submits proposed claim 16 to substitute original claim 1, proposed claim 17 to substitute original claim 8, proposed claim 18 to substitute original claim 9, and proposed claim 19 to substitute original claim 15. *Id*. Thus, the proposed claims 16–19 represent a one-for-one substitution for original claims 1, 8, 9, and 15, respectively.[13] Accordingly, we determine that Patent Owner has met the requirement of 37 C.F.R. § 42.121(a)(3).

B. Written Description Support

Pursuant to 37 C.F.R. § 42.121(b), a motion to amend in an *inter partes* review must set forth "[t]he support in the original disclosure of the patent for each claim that is added or amended," and "[t]he support in an

[13] Proposed substitute claims 16 and 18 are set forth as independent claims directed to a compound of Formula I. Proposed substitute claim 17 is directed to pharmaceutical composition comprising the compound of claim 16. Similarly, proposed substitute claim 19 is directed to a pharmaceutical composition comprising the compound of claim 18.

earlier-filed disclosure for each claim for which benefit of the filing date of the earlier filed disclosure is sought." In particular, the limitations added to the challenged claims must be supported *individually* by the application, from which Patent Owner claims priority, and the substitute claims also must be supported *as a whole* by that application. *Nichia Corp. v. Emcore Corp.*, Case IPR2012-00005, slip op. at 4 (PTAB June 3, 2013) (Paper 27).

The language of the proposed substitute claims does not need to be described *in ipsis verbis* in the original disclosure to support the proposed substitute claims. *Id.*; *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1323 (Fed. Cir. 2000); *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1570 (Fed. Cir. 1996). However, if the original disclosure does not use the precise terminology recited in a proposed claim, "mere citation to the original disclosure without any explanation as to why a person of ordinary skill in the art would have recognized that the inventor possessed the claimed subject matter as a whole may be similarly inadequate." *Nichia Corp.*, slip op. at 4. In other words, in such case, the question remains whether the disclosure reasonably would lead persons of ordinary skill in the art to the subject matter recited in the proposed claims. *See Fujikawa*, 93 F.3d at 1570.

Patent Owner asserts that each proposed claim finds written description support in the Applications. Amend Mot. 4–7. Specifically, Patent Owner asserts that the Applications each describe Compound 111, which discloses every limitation of proposed claims 16 and 18. *Id*. at 5. Additionally, Patent Owner asserts that the Applications also describe a pharmaceutical composition and a pharmaceutically acceptable carrier, as further recited in proposed claims 17 and 19. *Id*. at 7–8. We agree.

Petitioner disagrees only in a conditional manner. Amend Opp. 12. According to Petitioner, Concert improperly seeks to read particular "advantageous properties" of *in vitro* and *in vivo* KIE, and clinical profile into claims 16–19 by linking them to the claimed invention and asserting that a person of ordinary skill in the art would not have had a reasonable expectation of success in arriving at the claimed invention. *Id*.. Petitioner states that "[i]f, however, the 'claimed invention' is read to require 'advantageous properties' for the purposes of a reasonable expectation of success, it necessarily follows from this disclaimer that there must be written description and enabling support for these 'advantageous properties.'" *Id*. at 13. We need not address that conditional argument because, as Petitioner correctly asserts, such "advantageous properties" are not recited in the original or proposed substitute claims.

Accordingly, we determine that Patent Owner has met the requirement of 37 C.F.R. § 42.121(b).

C. Respond to a Ground of Unpatentability Involved in the Trial

"A motion to amend may be denied where: (i) The amendment does not respond to a ground of unpatentability involved in the trial . . . ." 37 C.F.R. § 42.121(a)(2)(i).

Patent Owner asserts that the proposed substitute claims respond to the asserted grounds of unpatentability in the *inter partes* proceeding. Amend Mot. 8. Specifically, Patent Owner asserts:

> The Substitute Claims respond to the asserted grounds because as of 2012, (1) there was an affirmative motivation for POSAs not to combine the asserted references to arrive at the Substitute Claims, (2) there was no reasonable expectation of success in combining the asserted references to produce the compound or composition of the Substitute Claims, and (3)

> objective indicia support nonobviousness of the Substitute Claims. As to objective indicia, Concert's CTP-543 product under development has demonstrated unexpected beneficial results and a likelihood of satisfying a long-felt need. There is a nexus between these unexpected results and the Substitute Claims, as CTP-543 has the isotopic purity recited in claim 18 and is Compound 111 (*see* Ex. 2001, ¶4; Ex. 2079, ¶10), which, as explained above (*supra* Section III), is claimed by proposed claims 16 and 18.

Id. at 8–9. Patent Owner asserts further that "nothing in the asserted grounds addresses the claimed isotopic purity of proposed claims 18 and 19." *Id*. at 9.

Petitioner asserts that Patent Owner's motion to amend should be denied because the proposed substitute claims do not respond to a ground of unpatentability involved in the trial. Amend Opp. 10. Patent Owner asserts that proposed claims 16–19 read on Compound 111, which was shown to have been obvious in the Petition as it was a basis for the obviousness grounds. *Id*. (citing Amend Mot. 5; Pet 8–9, 26–43, 50–55). According to Petitioner, Patent Owner "does not, and cannot, explain how still claiming that obvious compound is responsive to either ground." *Id*.

Petitioner asserts that, in the motion to amend, Patent Owner merely repeats the same arguments that it presented in the Patent Owner Response regarding the challenged original claims, and that, by doing so, Patent Owner reveals that claims 16–19 are not patentably distinct from the original claims. *Id*. at 11 (citing PO Resp. 46–71; Amend Mot. 8–25). Petitioner notes that Patent Owner "neither mentions nor relies upon the added limitations of claims 16–19 anywhere in its arguments on motivation or reasonable expectation of success beyond relying on CTP-543 as an embodiment just as it does in the POR." *Id*. (citing Amend Mot. 9–19; PO

Resp. 30–37, 46–66). Petitioner notes also that Patent Owner relies on the same evidence and arguments regarding secondary considerations in its motion to amend for the proposed substitute claims as it did for the original claims in the Patent Owner Response. *Id*. (citing PO Resp. 36–37; Amend Mot. 22–23). Further, Petitioner asserts that the motion to amend does not address how the added limitation in claims 18 and 19 regarding isotopic purity responds to a ground of unpatentability. *Id*. at 12.

Based upon our review of the arguments and evidence, we agree with Petitioner that the motion to amend does not set forth how the proposed substitute claims respond to the asserted grounds of unpatentability. Insofar as the proposed substitute claims narrow the compounds of the challenged original claims, they have done so in a manner that still covers the compound that we have found to be obvious over the ground involving the combined teachings of Rodgers, Shilling, and the Concert Backgrounder. Patent Owner asserts that the proposed claims are not obvious over that ground for the same reasons asserted in the Patent Owner Response regarding the original claims, without identifying how analysis of the proposed substitute claims would be distinguished. Nor do we see how they could be as the same compound, i.e., Compound 111/CTP-543, is relied upon to represent the original claims and proposed substitute claims. Further, as Petitioner asserts, Patent Owner refers to the additional isotopic purity limitation in proposed claims 18 and 19, i.e., "wherein each position designated specifically as deuterium has at least 95% incorporation of deuterium," without explaining or providing evidence how that additional limitation, also covered by Compound 111/CTP-543, responds to the ground of unpatentability.

Patent Owner explains, in the Reply to Petitioner's Opposition to the Motion to Amend, that the proposed substitute claims respond to the ground because, "to the extent that the Board determines that the unexpected results offered by Concert are not commensurate in scope with the broader, original claims of the '149 Patent, those results are commensurate in scope with the narrower substitute claims 16–19." Paper 84, 11–12. However, our determination that Patent Owner's evidence did not demonstrate unexpected results was not based upon that contention. Rather, we determined that the results represented a difference in degree and not in kind. The proposed substitute claims do not respond to that deficiency.

Accordingly, because we find that Patent Owner has not met the requirement in 37 C.F.R. § 42.121(a)(2)(i) by proposing substitute claims that do not respond to a ground of unpatentability in the trial, the Motion to Amend is denied.

V. CONCLUSIONS

For the foregoing reasons, we conclude that Petitioner has shown by a preponderance of the evidence that the challenged claims of the '149 patent are unpatentable as obvious over Rodgers, Shilling, and the Concert Backgrounder. Additionally, we conclude that Petitioner has not established that it is entitled to have Exhibits 2001, 2002, 2019, 2048, 2057, 2071, 2078, 2079, 2122, and 2123 excluded. We conclude Petitioner is entitled to exclude Exhibits 2099–2101, 2103, 2104, and 2112. We also conclude that Patent Owner has not met the requirements of 37 C.F.R. § 42.121(a)(2)(i) for amending claims.

ORDER

In consideration of the foregoing, it is hereby:

ORDERED claims 1–15 of the '149 patent are unpatentable under 35 U.S.C. § 103 as obvious over Rodgers, Shilling, and the Concert Backgrounder;

FURTHER ORDERED that Petitioner's Motion to Exclude is *denied* with respect to Exhibits 2001, 2002, 2019, 2048, 2057, 2071, 2078, 2079, 2122, and 2123, and *granted* with respect to Exhibits 2099–2101, 2103, 2104, and 2112;

FURTHER ORDERED that Patent Owner's Contingent Motion to Amend is *denied*; and

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

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Patent 9,249,149 B2

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