

Filed: October 18, 2018

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

NOVARTIS PHARMACEUTICALS CORPORATION

Petitioner,

v.

PLEXXIKON INC.,

Patent Owner.

Case IPR2018-01287
Patent Number: 9,469,640

**PRELIMINARY RESPONSE TO PETITION FOR *INTER PARTES*
REVIEW OF U.S. PATENT NO. 9,469,640**

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PATENT OWNER'S EXHIBIT LIST

EXHIBIT #	DESCRIPTION
2001	June 29, 2012 Office action filed in the prosecution of U.S. Application 12/669,450
2002	February 19, 2016 Preliminary Amendment filed in the prosecution of U.S. Patent No. 9,469,640
2003	July 16, 2016 Interview Summary filed in the prosecution of U.S. Patent No. 9,469,640
2004	James Tsai, et al., "Discovery of a selective inhibitor of oncogenic B-Raf kinase with potent antimelanoma activity", PNAS (2008) 105:8, 3041-3046.
2005	John C. Stellwagen et al., "Development of potent B-Raf ^{V600E} inhibitors containing an arylsulfonamide headgroup", Bioorganic & Medicinal Chemistry Letters 21 (2011) 4436-4440.
2006	Tara R. Rheault, et al., "Discovery of Dabrafenib: A Selective Inhibitor of Raf Kinases with Antitumor Activity against B-Raf-Driven Tumors", ACS Medicinal Chemistry Letters (2013), 4, 358-362.

Patent Owner Plexxikon Inc. (“Patent Owner”) submits this Preliminary Response in accordance with 35 U.S.C. § 313 and 37 C.F.R. § 42.107, in response to the Petition for *Inter Partes* Review (the “Petition”) filed by Novartis Pharmaceuticals Corporation (“Petitioner”) regarding Claims 1, 2, 4-6, 9, 11, and 12 of U.S. Patent No. 9,469,640 (“the ’640 patent”).

I. INTRODUCTION

The ’640 patent is directed to novel compounds, and methods of using such compounds, to treat diseases (such as melanoma, thyroid cancer, and colorectal cancer) associated with aberrant activity of protein kinases. Specifically, the claimed compounds treat diseases associated with a mutated version of the gene BRAF, which encodes for enzymes known as “BRAF kinases” that increase cellular metabolism and growth of cancer cells. The therapeutic compounds Patent Owner invented work by binding to the mutated BRAF kinase in a manner that inhibits its activity, thereby disrupting cancer cells’ ability to metabolize energy and proliferate.

Although BRAF kinase inhibitors existed prior to Patent Owner’s inventions, such prior art BRAF kinase inhibitors were not selective and therefore simultaneously inhibited many different kinases, resulting in severe side effects that prevented them from being used in doses that would most effectively fight cancer. In contrast, the novel selective BRAF kinase inhibitors developed by

Patent Owner have, at their core, a sulfonamide with its nitrogen adjacent to the fluorine in a fluorinated phenyl. When this core is coupled to six different substituents to give a molecule the proper overall shape and size, it will bind *selectively* to kinases resulting from the BRAF^{V600E} (or V600E BRAF) mutation. This mutation is frequently found in melanoma and to a lesser degree in other cancers.

The BRAF^{V600E} selectivity of Patent Owner's kinase inhibitors allows them to be given in much higher doses, resulting in a far more pharmacologically effective treatment than non-selective BRAF kinase inhibitors. Patent Owner's invention was a true scientific breakthrough that resulted in dramatic improvements for critically ill patients and immediately became the new standard of care for certain patients with metastatic melanoma who previously had very limited treatment options. To protect its invention, Patent Owner filed patent applications as early as June 22, 2005 that disclose the novel compounds responsible for selective BRAF kinase inhibition. Several of those applications matured into patents that cover selective BRAF kinase inhibitors, including the '640 patent.

The existence of Patent Owner's intellectual property, however, has not deterred Petitioner from utilizing Patent Owner's inventions. Indeed, in parallel district court litigation, Petitioner does not dispute that its accused product,

dabrafenib, infringes the '640 patent. That litigation is scheduled for trial in October 2019—well before completion of any trial in these proceedings.

Yet, Petitioner now asks the Board to institute IPR proceedings on the '640 patent. While the Petition purports to be based on alleged anticipatory prior art, this is not really an anticipation case because the art in question post-dates the priority date of the '640 patent. Rather, Petitioner contends that its infringing product anticipates the '640 patent because the challenged claims allegedly lack written description and enablement support such that they are not entitled to *any* priority date whatsoever. In this regard, the Petition is an unusual back-door attempt to present § 112 challenges in an IPR, which is forbidden by statute.

Even if Petitioner's § 112 challenges were statutorily cognizable, they are without merit. The Patent Office already considered the very § 112 arguments upon which Petitioner primarily relies during the lengthy prosecution history of the '640 patent, and allowed the claims only after being convinced that the claims, as amended, were fully supported under § 112. The Board should thus exercise its discretion to deny institution pursuant to § 325(d).

As to the merits, Petitioner does not dispute that the core structure that is undisputedly a key part of the invention and that appears in 120 individual chemical compounds disclosed in the '640 patent is both enabled and supported by adequate written description. Nor does Petitioner dispute that the specification

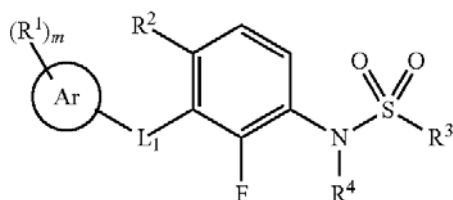
teaches six different substituents coupled to this core structure to yield compounds with a particular overall shape and size needed to selectively inhibit BRAF^{V600E} kinases. The only argument Petitioner raises is that two of the six different substituents used in the claimed invention are disclosed too broadly. And, of these two groups, Petitioner focuses on just one of them: the linker L₁ as a bond.

Yet, the specification unambiguously describes compounds in which L₁ is a bond (including in formula Ic) and details precisely how to make such compounds using the Suzuki reaction, which was invented in 1978 and is so versatile and powerful it was the subject of the 2010 Nobel Prize in chemistry. The fact that Petitioner's main arguments about lack of possession and undue experimentation focus on an old, widely known chemical reaction that is expressly disclosed in the specification is a red flag that the Petition lacks merit. As documented below, the challenged claims are amply supported under § 112 and Petitioner respectfully submits that the Board should deny institution.

II. BACKGROUND

Further to the above background, the compounds disclosed and claimed in the '640 patent require a core structure consisting of a fluorinated phenyl with the fluorine adjacent to a sulfonamide, and various substituents connected thereto yielding molecules with a particular overall shape and size. Representative claim 1 of the '640 patent is reproduced below:

1. A compound of formula (Ia):



or a pharmaceutically acceptable salt thereof,
wherein:

L_1 is a bond or $-N(H)C(O)-$;

each R^1 is optionally substituted lower alkyl or optionally substituted heteroaryl;

R^2 is hydrogen or halogen;

R^4 is hydrogen;

R^3 is optionally substituted lower alkyl or optionally substituted aryl;

m is 0, 1, 2, 3, 4, or 5; and

Ar is a monocyclic heteroaryl containing 5 to 6 atoms wherein at least one atom is nitrogen.

Petitioner's § 112 attacks focus on two aspects of this claim: the linker L_1 and, to a lesser extent, the R^1 substituent group. The linker L_1 connects the core structure of the claimed invention to the monocyclic heteroaryl group, while the R_1 group describes the substituents that may be on the heteroaryl group.

III. ARGUMENT

A. The Petition Is A Back-Door Effort To Challenge Validity Under § 112 In Violation Of The AIA

The Petition should be denied under 35 U.S.C. § 311 because it is an improper attempt to challenge the '640 patent under 35 U.S.C. § 112 in an IPR. Specifically, Petitioner's sole purported ground of unpatentability is predicated on a determination that the challenged claims are not entitled to the P2 priority date because its specification does not provide § 112 support for the challenged claims.¹

Critically, this is not a situation where Petitioner is asking the Board to determine the proper priority date in a chain of provisionals, continuations-in-part, and/or divisionals. Rather, the '640 patent is one patent in a chain of *continuations*, all of which undisputedly share an *identical* disclosure. Thus,

¹ The '640 patent is entitled to claim priority to not just P2, but also P1 because each application in the priority chain of the '640 patent is a continuation and thus shares the identical disclosure. While Patent Owner refers to P2 because Petitioner contends that the '640 patent is not entitled to claim priority to P2, nothing in this response should be construed as an admission that the '640 patent is unable to claim priority to P1.

Petitioner's request for a "priority" determination is nothing other than a request that the Board invalidate the challenged claims under § 112. While the Petition is styled as an anticipation challenge, it would be pointless for the Board to actually address the "anticipation" issue if it decides the predicate § 112 issue in Petitioner's favor.

This sort of "priority" argument is not statutorily cognizable under § 311(b), which provides that in an IPR, a petitioner "may request to cancel as unpatentable 1 or more claims of a patent ***only on a ground that could be raised under section 102 or 103.***" In other words, Petitioner asks the Board to determine substantive § 112 arguments that it does not have authority to adjudicate. *See Cuozzo Speed Techs. LLC v. Lee*, 136 S. Ct. 2131, 2141-42 (2016) ("nor does our interpretation enable the agency to act outside its statutory limits by, for example, canceling a patent claim...under § 112 in *inter partes* review. Such 'shenanigans' may be properly reviewable in the context of § 319...which enables reviewing courts to 'set aside agency action' that is... 'in excess of statutory jurisdiction[.]'" (citation omitted).

While the Board has considered § 112 arguments in the context of genuine priority disputes in IPR petitions, to do so here would set a poor precedent inconsistent with governing law.

First, instituting IPR based on these grounds for continuation patents would lead to countless § 112 attacks in IPRs. For example, accused infringers in district court litigation could simply challenge “priority” under § 112 to assert their infringing products as anticipatory prior art references.

Second, IPR petitioners should not be permitted to evade the requirements of § 311(b) by cloaking their § 112 attack as a “priority” dispute. This would not only violate the express language of § 311(b), but it would subvert the distinction between post grant review (“PGR”)—which permit § 112 validity challenges—with IPRs that do not. This result contravenes the statute and intent of Congress in limiting IPRs to prior art-based attacks.

Finally, if the Board were to institute the Petition, but ultimately resolve the § 112 issue in Patent Owner’s favor, Petitioner could circumvent the estoppel provisions of section 315(e) by relying on the very prior-art-only language of § 311(b) to argue that estoppel does not apply to Petitioner’s § 112 arguments. The unsuccessful petitioner could then attempt to re-litigate the § 112 grounds it lost in the IPR and unfairly subject Patent Owner to the same challenges in multiple proceedings, in contravention of the statutory estoppel provisions,.

For these reasons, the Board should deny institution because Petitioner’s “priority” challenge is not statutorily cognizable. As a result, the Petition fails to cite any prior art under § 102, as Petitioner’s sole alleged prior art reference was

published five years after the 2007 priority filing of the '640 patent. Patent Owner thus respectfully submits that institution can be denied on this ground alone.

B. The Board Should Exercise Its Discretion To Deny Institution Pursuant To § 325(d)

Under § 325(d), the Board has discretion to deny institution because “the same or substantially the same prior art or arguments previously were presented to the Office.” *Praxair Distrib., Inc. v. INO Therapeutic LLC*, IPR2015-00893, Paper 14 at 8 (P.T.A.B. Sept. 22, 2015). In determining whether to exercise this discretion, the Board considers, *inter alia*, the extent of the overlap between the arguments presented in the Petition and considered by the Examiner during prosecution, as well as whether any additional evidence and facts presented in the Petition warrant reconsideration of such arguments. *See Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 at 17-18 (P.T.A.B. Dec. 15, 2017).

As demonstrated below, these considerations overwhelmingly and independently counsel against institution. Not only did the Examiner explicitly consider the § 112 support for the challenged claims in prosecution, but the Examiner addressed head-on the specific arguments about the L₁ substituent, which are now at the heart of Petitioner’s case. These issues were so central during prosecution that the Patent Owner amended claims specifically to overcome

the Examiner's § 112 rejections. On these facts, there can be no dispute that the prosecution history of the '640 patent favors denial of institution.

1. § 112 Was Repeatedly Considered During Prosecution

During the prosecution of the '640 patent, the Examiner extensively considered the § 112 support for the pending claims and rejected the claims several times because they “read on numerous possible distinct species [and] there is no substantial feature shared by all species.” Ex. 2001 at 4. This argument mirrors the very arguments Petitioner now presents. The Examiner rejected pending claims that are very similar in scope to the challenged claims, citing arguments that are virtually identical to those advanced by Petitioner, and ultimately Patent Owner overcame the Examiner's concerns.

During prosecution of P4, Patent Owner submitted claims strikingly similar in scope to the challenged claims and the Examiner issued a rejection under § 112 that is nearly identical in substance to the arguments now raised by Petitioner:

The only disclosure, is in the form of general formula with lists of possible groups....This kind of disclosure is not representation of any species. A “laundry list” of every possible moiety does not constitute a written description of every species in a genus because it would not “reasonably lead” those skilled in the art to any particular species.

Ex. 1008 at 6-7. In his § 112 analysis, the Examiner, like the Petitioner here, focused on the L₁ substituent:

All disclosed compounds have a linker moiety between the phenyl and the Ar. i.e., L1 in formula 1 is not a bond. The application provide no convincing evidence, or rationale that the biological activity of the disclosed compounds would have been retained if the L1 in formula 1 is a bond instead of those linking moieties.

Id. at 7.

In response to this rejection, the Applicant amended the claims to be directed to a more focused genus of compounds claiming L₁ as, *inter alia*, a bond, and identified where its amendments found support in the specification under § 112. Ex. 1009 at 2-5. The Examiner initially maintained his § 112 rejections, reiterating that the specification did not provide § 112 support for the claimed compound genus. Ex. 1010 at 10.

In a subsequent interview, however, the Applicant pointed to numerous embodiments throughout the specification that supported the pending claims under § 112, and the Examiner then ***agreed*** that the application had support for L₁ as an amide or a bond. Ex. 1011 at 1. Although the Examiner maintained his rejections on other grounds, the issue of whether the specification had support for L₁ was resolved in Applicant's favor. Ex. 1012 at 1-4. The Applicant then abandoned P4 in favor of P5.

During the prosecution of P5, which eventually issued as the '640 patent, the Applicant filed new claims. In the process, the Applicant specifically identified

support for the claims in the priority applications. Ex. 2002 at 3-7. Although the Examiner initially rejected the claims for failing to comply with § 112, Ex. 1015 at 3-7, in a subsequent interview the Applicant and Examiner again discussed “the scope of the claimed invention that has sufficient written description support from the application...Particularly, the scopes of Ar and L₁.” Ex. 2003 at 1. The Applicant amended its claims to address the Examiner’s concerns, and identified specific support for the amendments in the specification. Ex. 1016 at 2-7.

Consistent with the Examiner’s conclusion during prosecution of P4, the Examiner allowed the claims, stating that “[t]he amendments of the claims, limiting the Ar in general formula (Ia) to monocyclic heteroaryl, **and the L₁ is limited to a bond or –N(H)C(O)– is sufficient to overcome the rejections under 35 U.S.C. § 112, first paragraph**, as set forth in the prior office action.” Ex. 1017 at 6. It is thus clear that the Examiner carefully considered whether there was adequate support under § 112 for the claims, and ultimately concluded that there was, including with regard to the very claim element upon which Petitioner now focuses its invalidity arguments.

2. The Prosecution History Strongly Supports Denial Of The Petition Under Section 325(d)

Petitioner advances § 112 arguments that are entirely cumulative to those the Office considered extensively during prosecution. Petitioner offers no new evidence to warrant revisiting the Examiner's findings that § 112 is satisfied.² Specifically, as documented above, during the years of prosecuting the '640 patent the Examiner rejected the claims as allegedly unsupported by § 112. Patent Owner specifically overcame these rejections by providing argument and amending the claims to their present form, and the Examiner explicitly found the Applicant's § 112 arguments persuasive when he ultimately allowed the claims.

Faced with this record, Petitioner's primary response is that the Applicant's abandonment of certain applications while § 112 rejections were pending

² Dr. Baran's expert declaration submitted in support of the Petition does not present any new evidence that would warrant revisiting the Office's determination. Many of Dr. Baran's conclusions are unsupported by any evidence regarding what was known to POSITAs at the time of the invention. Dr. Baran's declaration simply parrots the Petition in form, substance, and verbiage throughout and should be given no independent weight.

demonstrates the merit of the § 112 rejections. See Petition at 3. Yet, abandonment and filing of a continuation does not give rise to any presumption regarding the merits of arguments pending at the time of abandonment, and Petitioner cites no authority to support such an extreme proposition.³

Moreover, Petitioner cannot dispute that the Office fully considered and vetted the § 112 support for the claims, allowing them only after they were amended to specifically address the very issues now raised by Petitioner. See *Sanofi-Aventis U.S., LLC v. Immunex Corp.*, IPR2017-01129, Paper 19 at 10 (P.T.A.B. Oct. 4, 2017) (denying institution based on priority challenge given Petitioner's failure to address the Office's priority determination and the effect of that determination on Petitioner's challenge).

The Board has exercised its discretion to deny institution based on facts similar to those here. For example, in an informative decision, *Hospira, Inc. v. Genentech, Inc.*, IPR2017-00739, Paper 16 (P.T.A.B. Jul. 27, 2017), the Petitioner's sole invalidity challenge was predicated on a determination that the challenged claims were not entitled to the priority date of the provisional

³ Because the claims in P4 differ in scope from those in P3, and are commensurate with the specification disclosure, the § 112 rejection in P3 is moot.

application because it did not provide § 112 support for the challenged claims. *Id.* at 18-19.

The Office, however, had already considered the § 112 support provided by the priority application during prosecution of the challenged patent. *Id.* at 8-13. Specifically, the Examiner had rejected the originally filed and subsequently amended claims of a continuation application several times under § 112 because the priority application purportedly did not provide support for the pending claims. *Id.* Because the application was not entitled to the benefit of the earlier filing date, the Examiner had rejected the pending claims under § 102(b) as anticipated by a prior art reference. *Id.* at 8-9. The Applicant overcame the Examiner's § 112 rejections by amending its claims in accordance with the Examiner's comments and by providing argument explaining where the claims found support in the specification. *Id.* at 9-11.

In denying institution, the Board in *Hospira* considered this prosecution history and found that the Petitioner did not present “any further evidence in this proceeding that would persuade us to reach a conclusion different from the Examiner's position that the challenged claims are adequately disclosed in the priority document.” *Id.* at 14.

The same is true here. As explained above, the Office has already decided the dispositive § 112 issue and Petitioner has not presented any new argument or

evidence to justify reaching a different conclusion. In these circumstances, it would be wasteful to revisit the same § 112 issues the Office carefully considered. *See, e.g., Neil Ziegman, N.P.Z., Inc. v. Stephens*, IPR2015-01860, Paper 11 at 13-14 (P.T.A.B. Feb. 24, 2016) (denying institution under § 325(d) because it was not “an efficient use of Board resources” to address “an issue already and unambiguously presented previously to and considered by the Office” during prosecution). The Board should thus deny institution pursuant to § 325(d).

C. Petitioner’s Invalidity Arguments Fail On The Merits

For the reasons stated above, Petitioner’s § 112 arguments are not statutorily cognizable and need not be rehashed after being thoroughly dealt with during prosecution. Yet, even if the Board considers Petitioner’s written description and enablement arguments on the merits, they fail both legally and factually.

1. The Written Description Requirement Is Satisfied

Briefly, Petitioner’s written description challenge is that the specification discloses broad genera of compounds but fails to sufficiently direct a POSITA to the particular compounds recited in the claims. According to Petitioner, this “is a quintessential case of a patentee disclosing a ‘forest’ in P2 and later claiming a ‘tree’....” Petition at 14. Such allegations are without merit.

The reasons why this is so are straightforward and are summarized as follows:

- The '640 patent discloses chemical formulae commensurate with the claims, such that the written description requirement is satisfied as a matter of law.
- The '640 patent also includes representative species and descriptive “blaze marks” directly guiding a POSITA to the claimed compounds, further establishing that there is adequate written description.
- Given the historical record—particularly the technical publications of its predecessor in interest—Petitioner cannot dispute that these “blaze marks” point to key identifying features of the claimed compounds that distinguish them from other compounds.
- Thus, almost all of Petitioner’s arguments are ultimately based on two variables of the disclosed and claimed compounds. Such arguments, however, are based on a legally erroneous understanding of the written description requirement and fail as a matter of law.

Each of these points is addressed in turn below.

a. Generic Formulae Establish That The Written Description Requirement Is Satisfied

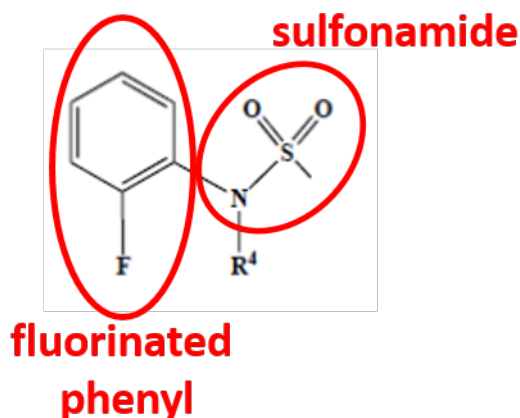
It is noteworthy that Petitioner cites almost no law in support of its position. *See generally* Petition at 14-41. Indeed Petitioner fails to address the fact that, for chemical compounds, the law is clear that generic formulae may be used to satisfy the written description requirement for a claimed genus:

In claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus.

Regents of the Univ. of California v. Eli Lilly & Co., 119 F.3d 1559, 1568 (Fed. Cir. 1997), *aff'd in part, rev'd in part*, 457 F.3d 1284 (Fed. Cir. 2006); *see also Pfizer Inc. v. Ranbaxy Labs. Ltd.*, 405 F. Supp. 2d 495, 505 (D. Del. 2005) (citing *Eli Lilly*, holding written description requirement satisfied where “the written description of the ’893 patent is a generic formula which the patent specification expressly indicates includes all trans-enantiomers”). The Patent Office recognizes in its manual for patent examiners that this is the correct standard. *See, e.g.*, M.P.E.P. § 2163 (citing *Eli Lilly*, explaining that “a formula is normally an adequate description of the claimed genus”).

Applying this standard—which Petitioner ignores—there can be no dispute that the challenged claims satisfy the written description requirement. This is because the specification discloses generic formulae Ib and Ic, the combination of which disclose compounds directly commensurate with the claims.

To begin, both formulae Ib and Ic include the **exact** core structure set forth in the claims, which consists of a fluorinated phenyl with the fluorine adjacent to a sulfonamide:



Likewise, the scope of the claimed substituents (L_1 , R^1 , R^2 , R^3 , R^4 , m , and Ar) attached to this core structure is directly commensurate with the combination of formulae Ib and Ic:

- In the claims, L_1 can be $-N(H)C(O)-$ or a bond. Formula Ib is limited to L_1 as $-NR^{11}A-$, with A having just two general options, one of which is $-C(O)-$, and further explains that R^{11} is “preferably H.” This corresponds to $-N(H)C(O)-$. See Ex. 1001 at 5:45, 5:54-55. And formula Ic is limited to L_1 as a bond. See *id.* at 6:40-49.
- As to R^1 , the claims recite “optionally substituted lower alkyl” and “optionally substituted heteroaryl” as options. Both of these are disclosed in formulae Ib and Ic as choices from a Markush group of well-known chemical substituents. See *id.* at 1:66-2:10, 5:47-48, 6:50-51.

- As to R², the claims recite “hydrogen, lower alkyl or halogen,” and both formulae Ib and Ic disclose “hydrogen, lower alkyl, or halogen.” *Id.* at 2:14, 5:47-48, 6:50-51. Further, formula Ib discloses particular embodiments where R² is “hydrogen, fluoro or chloro.” *Id.* at 5:56. Likewise, Formulae Ic discloses that R² is “hydrogen, fluoro or chloro.” *Id.* at 6:58.
- For R⁴, the claims recite “hydrogen,” while formulae Ib and Ic disclose “hydrogen or lower alkyl” as options. *See id.* at 2:32-33, 5:47-48, 6:50-51. Formulae Ib further specifically explains that “preferably R⁴ and R¹¹ are H,” while formulae Ic states that “preferably R⁴ is H.” *Id.* at 6:3, 6:57.
- As to R³, the claims recite “optionally substituted lower alkyl” or “optionally substituted aryl,” which are both listed in formulae Ib and Ic as choices from a limited set of options. *See id.* at 2:17-20, 5:47-48, 6:50-51.
- As to m, the claims recite 0, 1, 2, 3, 4, or 5, and formulae Ib and Ic recite m=0, 1, 2, 3, 4, or 5. *See id.* at 2:11, 5:46-48, 6:50-51.
- Finally, the claims recite that Ar is a “monocyclic heteroaryl containing 5 to 6 atoms wherein at least one atom is nitrogen,” while formulae Ib and Ic recite that Ar may be “optionally substituted heteroaryl.” *Id.* at claims 1, 11, 21 and 1:65, 5:47-48, 6:50-51.

As the foregoing shows, Petitioner's position that there is some extraordinary gap between the scope of the disclosure and the scope of the claims is simply incorrect. The claims are plainly commensurate with formulae Ib and Ic in the specification. Indeed, although there are six different substituents, Petitioner only contends that there is a meaningful written description defect with regard to two of them (L_1 and R^1). *See generally* Petition at 14-41. The fact that Petitioner can muster an argument for **only two** variables is a compelling indicator of just how well supported the claims are.

Importantly, formulae Ib and Ic are set forth not in functional terms, but as unambiguous chemical structures with clear boundaries, thus demonstrating as a matter of law that the inventors necessarily envisioned and possessed the chemical compounds within their scope, including all of the claimed compounds. While the combination of formulae Ib and Ic is somewhat broader than the claims, any such differences are modest and do not indicate a lack of written description, as confirmed by governing law regarding chemical compound patents.

Specifically, in *In re Driscoll*, the patent at issue disclosed a Markush group with fourteen options, while only one of these fourteen options was claimed. *See In re Driscoll*, 562 F.2d 1245, 1246-47 (C.C.P.A. 1977). The Court held that this 14:1 ratio did not present any § 112 problem. *See id.* at 1249 (It "follows that S.N. 782,756 describes the subject matter of claim 13 inasmuch as one of the fourteen

classes of compounds is the 5-alkylsulfonyl-1, 3, 4-thiadiazole ureas defined therein.”).

By comparison, the variables L_1 and R^1 that Petitioner contends are inadequately described have an even smaller ratio than the 14:1 ratio deemed to be sufficient in *Driscoll*. For R^1 , this ratio is 23:2 (23 total possible substituents, of which two are claimed).⁴ And, for L_1 , there are three disclosed options in formulae 1b and 1c, two of which (a bond and -N(H)C(O)-) are claimed. Again, this 3:2 ratio is far narrower than the 14:1 ratio in *Driscoll*. This simple comparison alone establishes that there is no written description problem with the '640 patent.

Yet, perhaps more compelling is the Court's analysis and reasoning in *Driscoll*. Most important, the Court in *Driscoll* expressly distinguished in *In re Ruschig*, 379 F.2d 990 (C.C.P.A. 1967), which is one of Petitioner's primary cases. See *In re Driscoll*, 562 F.2d at 1250. In *Ruschig*, the specification disclosed a

⁴ Specifically, in the claims, there are two options for R^1 : “optionally substituted lower alkyl” and “optionally substituted heteroaryl.” In the specification there are just 23 total options for R^1 , a point Petitioner acknowledges. See Petition at 36 (“ R^1 is selected from a group consisting of 23 options...”). These 23 options are recited in formulae Ib and Ic. See Ex. 1001 at 1:66-2:10, 5:47-48, 6:50-51.

broad genus of chemical compounds via a generic formula and “an imaginary specific example”, but claimed only a *single* chemical compound. *See Ruschig*, 379 F.2d at 991, 993-95. Specifically, *Ruschig* “involved a copied claim (another inventor’s claim copied into Ruschig’s application)” to provoke an interference. *Union Oil Co. of Cal. v. Atl. Richfield Co.*, 208 F.3d 989, 1000 (Fed. Cir. 2000). This claim “did not find support in Ruschig’s application because Ruschig had invented and disclosed a broad set of the compounds that was similar, but not entirely within the scope of the claim. Because another inventor, not Ruschig, drafted the claim at issue to fit another specification, it is not surprising that the disputed claim did not find support in Ruschig’s specification, even though the inventions were similar.” *Id.*

Here, by contrast, the claims reflect the Patent Owner’s own invention as set forth in the specification, not claims corresponding to someone else’s invention that were copied to provoke an interference. *See infra* Part I.A.1.c. Moreover, the claims at issue here are not directed to a single chemical compound, but a genus of chemical compounds legally commensurate under § 112 with formulae Ib and Ic. In other words, this is not a situation where Patent Owner disclosed a “forest” and claimed a “tree.” Patent Owner disclosed a group of compounds and then claimed a commensurate group.

The type of analysis that was necessary in *Ruschig* to determine whether the specification supported a claim to a **single** chemical compound is thus inapplicable here. See *In re Ruschig*, 379 F.2d at 994 (“Specific claims to **single compounds** require reasonably specific supporting disclosure....”).⁵ Rather, the type of analysis that is required here, where the claims are commensurate in scope to the specification as filed, is the type of analysis applied in *Driscoll*, which considers whether a claimed sub-genus is easily discerned from the specification:

Any seeming similarity between *Ruschig* and the present case is illusory, however, because the structural formula there relied on could have described, at best, only a subgenus including the specific compound claimed, **and not the compound itself**. In this respect, *Ruschig* is readily distinguishable from the present case where **the exact subgenus claimed is clearly discernible in the generalized formula** [that was disclosed].

In re Driscoll, 562 F.2d at 1250. This reasoning is directly on point here. The claims of the '640 patent are directed to a sub-genus that—for the reasons documented above—is “clearly discernable” in the generalized formulae (*e.g.*, formulae Ib and Ic) set forth in the specification.

⁵ Emphasis supplied unless otherwise noted.

Petitioner's attempt to have the Board analyze the sub-genus claims of the '640 patent using the approach set forth in *Ruschig* for claims directed to a single compound is off base. Indeed, as the Federal Circuit made clear long ago in *Utter v. Hiraga*, a "specification may, within the meaning of 35 U.S.C. § 112 ¶ 1, contain a written description of a ***broadly claimed invention without describing all species that claim encompasses.***" 845 F.2d 993, 998-99 (Fed. Cir. 1988). Because the specification here discloses well-defined genera through formulae Ib and Ic, the written description requirement is satisfied for the genus claims that are commensurate with these formulae.

b. The Specification Includes Extensive "Blaze Marks" To The Identifying Features Of The Compounds And The Claimed Substituents

Given the generic formulae, there is no written description problem for the challenged claims. Yet, even if these formulae were not present, the written description requirement would still be satisfied. This is because although the use of generic formulae is one path to satisfy the written description requirement for chemical compound claims, the Federal Circuit has made clear that another path is the disclosure of relevant identifying characteristics that distinguish chemical compounds from other compounds.

Notably, this path is available to inventors even if they did not have an accurate picture of the entire chemical structure or only had a ***partial structure*** for

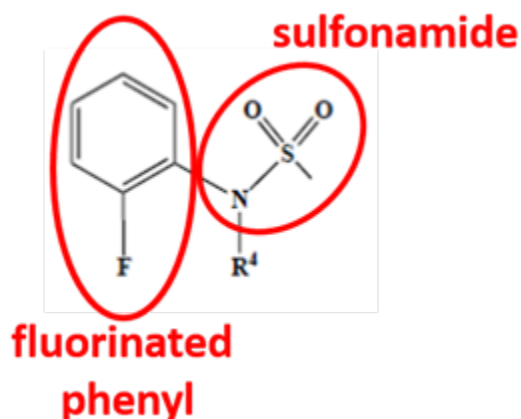
the compound. *See, e.g., Cubist Pharm., Inc. v. Hospira, Inc.*, 805 F.3d 1112, 1120 (Fed. Cir. 2015) (“It was enough that the specification disclosed **relevant identifying characteristics** that distinguished daptomycin from other compounds and thus showed that the inventors had possession of daptomycin, even though they may not have had an accurate picture of the entire chemical structure of that compound.”); *Invitrogen Corp. v. Clontech Labs., Inc.*, 429 F.3d 1052, 1072 (Fed. Cir. 2005) (written description satisfied “by disclosure of sufficiently detailed, **relevant identifying characteristics...i.e., complete or partial structure**, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics”); *see also Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1206 (Fed. Cir. 1991) (conception of invention complete by mental picture of “the structure of the chemical, or is able to define it by its method of preparation, its physical or chemical properties, or **whatever characteristics sufficiently distinguish it.**”).⁶

⁶ This is also the standard that the Patent Office has adopted in the M.P.E.P., explaining that if “the application does not describe an actual reduction to practice or reduction to drawings or structural chemical formula as discussed above,

Here, Patent Owner disclosed not just the general overall chemical structure needed to inhibit BRAF^{V600E} kinases through generic formulae, but also provided extensive additional disclosure pointing a POSITA to a specific conserved core structure for the claimed compounds. While Petitioner repeatedly asserts that there are no such “blaze marks” in the specification, *see* Petition at 2, 14-15, 25, 27, 29, 40, this case is noteworthy for the extent to which the specification points to such distinguishing features.

Most important, virtually every genus, species, and example in the specification is directed to a compound with a specific core structure consisting of a fluorinated phenyl with the fluorine adjacent to a sulfonamide group, as depicted below:

determine whether the invention has been set forth in terms of ***distinguishing identifying characteristics*** as evidenced by other descriptions of the invention that are sufficiently detailed to show that applicant was in possession of the claimed invention.” M.P.E.P. § 2163.



See, e.g., Ex. 1001 at Formulas Ib, Ic, If, Ih, Ij. Although a few genera in the '640 patent are somewhat broader than this structure, it is nonetheless within the scope of every single described genera. Every single compound disclosed in the specification includes this core structure. There are **120** such compounds in the specification. *See id.* at P-0001 through P-0120.

Likewise, the claimed chemical compounds include a uniform overall shape and size. This shape and size is immediately apparent by a quick glance at the generic formulae Ia-Ij disclosed in the specification, and indeed matches up with the overall structure utilized in the claims, which is recited using formula Ia. *See* Ex. 1001 at claim 1 ("A compound of formula (Ia). . .").

Both the conserved core structure and the overall shape and size of the compounds to which the '640 patent overwhelmingly points represent key identifying features of the invention. *See infra* Part I.A.1.c. As documented below, the scientific publications of Petitioner's predecessor, GSK, and the

structure of Petitioner's infringing product leave no room for Petitioner to argue otherwise.

It is noteworthy that **none** of Petitioner's written description arguments are directed to these key identifying features of the invention. Because there is no dispute that the specification discloses such identifying characteristics, there is no written description problem. See *Cubist*, 805 F.3d at 1120; *Invitrogen*, 429 F.3d at 1072; *Amgen*, 927 F.2d at 1206.⁷

In these circumstances, Petitioner attempts to make a written description argument by focusing on a couple of the variables affixed to the core structure of the '640 patent. In particular, Petitioner argues that there "are no blaze marks in P2 that point one of ordinary skill to the specific combination of claimed L₁ and R¹ substituent." Petition at 27. Even if Petitioner were correct that such alleged defects could constitute a legally cognizable written description problem, its

⁷ Petitioner does not address any of the law establishing that, in the context of patents on chemical compounds, the written description requirement is satisfied by the disclosure of the precise sorts of identifying characteristics set forth in the '640 patent. This is just one of many examples of how the Petition is premised on an unduly restrictive and erroneous view of the written description requirement.

contention that there are no “blaze marks” to the claimed L_1 and R^1 substituents is simply wrong.

First, for the linking moiety L_1 , the claims recite that it can be $-N(H)C(O)-$ or a bond. For $-N(H)C(O)-$, generic formulae Ib and Id expressly disclose this as one out of only a few options. *See* Ex. 1001 at 6:5-12, 7:36-45. What’s more, the specification discloses 40 individual chemical compounds where L_1 is $-N(H)C(O)-$. *See id.* at 76:1-20, 78:49-60, 79:55-80:33, 81:12-22, 82:48-57, 84:50-90:53, 91:36-47, 93:10-12, 93:56-95:13, 96:1-10, 107:8-17. With 40 individual chemical compounds disclosed in the specification, Petitioner does not even attempt to contend that there is a meaningful written description defect with regard to L_1 as $-N(H)C(O)-$.

Rather, for the linker L_1 , Petitioner focuses on L_1 as a bond. But again there are ample “blaze marks” in the specification. Formulae Ic and Ie, for instance, expressly disclose L_1 as a bond. *See id.* at 6:40-47, 8:5-12. Any suggestion that a POSITA would not be directed to these embodiments or might overlook them is belied by the fact that the specification further includes a detailed synthetic scheme

for preparing them based on the use of a Suzuki reaction. *See id.* at 71:56-67.⁸ Petitioner acknowledges that this scheme was “widely used in the pharmaceutical industry.” Petition at 45. Where, as here, Patent Owner has expressly disclosed a particular chemical substituent and a protocol for preparing that substituent, it is not credible to assert that Patent Owner was not in possession of that substituent for use without the invention.

Similar arguments apply to claimed embodiments where R¹ is an optionally substituted heteroaryl or optionally substituted lower alkyl. Every generic formula in the specification discloses these as options for R¹. *See, e.g.*, Ex. 1001 at 1:66-2:5, 5:47-48, 5:50-51. Likewise, the specification expressly teaches that R¹ can be heteroaryl that may be optionally substituted with 1, 2, 3, 4, or 5 substituents. *See id.* at 48:51-49:7. There are three species in the specification that include R¹ as an optionally substituted lower alkyl, including an example where m=2. *See id.* at 94:12-22, 94:40-55, 97:15-23.

⁸ Petitioner cannot deny the import of this disclosure, and thus tries to contend that it somehow does not enable L₁ as a bond. As documented below, however, the Suzuki reaction disclosed in the specification undoubtedly enables the POSITA to create the claimed compounds where L₁ is a bond. *See infra* Part I.A.1.e.

Beyond this, there are numerous examples in the specification exemplifying a breadth of options for R¹. *See, e.g., id.* at 76:1-20 (P-0011, where R¹ is a substituted heteroaryl linked to a NH group); *id.* at 78:50-60 (P-0005, where R¹ is a substituted lower alkyl linked to a NH group); *id.* at 79:55-80:11 (P-0009 and P-0015 where R¹ for both compounds is a cycloalkyl linked to a NH group); *id.* at 80:23-33, (P-0017, where R¹ is aryl linked to a NH group); *id.* at 80:13-22 (P-0016, where R¹ is a heteroaryl linked to a NH group); *id.* at 81:10-25 (P-0004, where R¹ is an acetyl linked to a NH group); *id.* at 94:1-10 (P-0003, where R¹ is a lower alkoxy); *id.* at 94:14-22 (P-0007, where both R¹ are lower alkyl); *id.* at 94:24-38 (P-0012, where R¹ is a substituted aryl); *id.* at 94:40-55 (P-0014, where R¹ is a substituted lower alkenyl). Any contention that the inventors were not in possession of the full-breadth of claimed R¹ options is without merit.

In short, the specification includes “blaze marks” not just to an identifying core structure, but also the substituents for this structure. The written description requirement is thus satisfied.

c. Petitioner Cannot Deny That The Specification Discloses “Blaze Marks” To The Relevant Identifying Characteristics Of The Invention

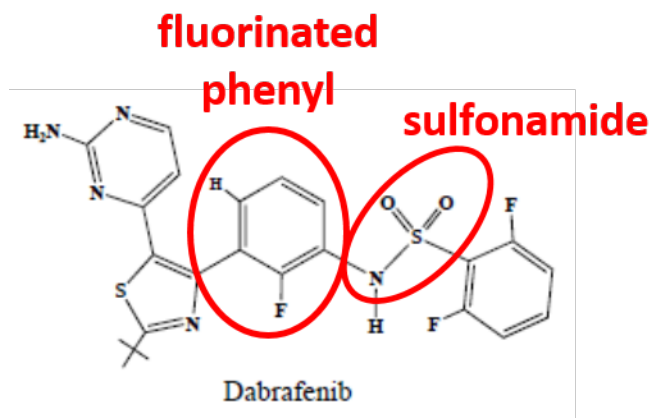
As shown above, the specification includes “blaze marks” pointing a POSITA to the features of the claimed compounds that distinguish them from other compounds, in particular the core structure consisting of a fluorinated phenyl with

the fluorine adjacent to a sulfonamide. Petitioner focuses all its energy on the linker L₁ and the routine chemical substituents for R¹ and does not dispute that the core structure and claimed overall shape and size are both enabled and supported by sufficient written description.

There is good reason for this. Specifically, Petitioner's predecessor-in-interest, GSK, repeatedly lauded the core structure in scientific publications, documenting the scientific underpinning for why it is uniquely effective as a kinase inhibitor. As such, the historical record leaves no room for Petitioner to challenge the distinguishing nature of the core structure disclosed in the '640 patent.

Patent Owner first published its core structure on January 4, 2007, in international patent application publication WO2007/002433. This was followed with an article in the Proceedings of the National Academy of Sciences (PNAS) on February 26, 2008, disclosing the core structure of the '640 patent and discussing the importance of this structure in selectively binding with the BRAF kinase produced due to the V600E mutation. The article explained that "[t]he critical binding determinant for oncogenic selectivity derives from the interaction between the *sulfonamide* and the beginning of the DFG region that subsequently directs the attendant alkyl chain into a small pocket unique to the Raf family." Ex. 2004 at 2.

Later, when GSK brought its infringing product, dabrafenib, to market, it incorporated the same exact core structure claimed in the '640 patent, as shown below:



Just like the 120 individual chemical compounds in the '640 patent, the core structure includes a sulfonamide for binding to the kinase that results from the BRAF^{V600E} mutation, and a fluorinated phenyl that acts to stabilize the binding interaction. It also includes the exact same overall shape and size, as confirmed by a quick comparison of dabrafenib to any one of generic formulae Ia through Ij disclosed in the '640 patent.

GSK then published multiple scientific articles disclosing the core structure of the '640 patent and acknowledging its importance and unique utility as a selective BRAF inhibitor. For instance, in June 2011, GSK published an article stating that “[e]valuation of several different headgroup linkers...revealed that the sulfonamide-containing analog showed a substantial improvement in cellular

potency, particularly in the pERK mechanistic assay run in B-Raf^{V600E} mutant SKMEL28 cells...***Thus, the sulfonamide N-H appeared to be a key pharmacophore for potent in vitro activity in this series.***” Ex. 2005 at 2-3. In this same article, GSK referenced Patent Owner’s compounds, stating that “[t]his is similar to the binding modes observed for the sulfonamide groups in the B-Raf inhibitors PLX4720 and PLX4032.” *Id.* at 3. PLX4720 and PLX4032 are the same BRAF inhibitors invented by Patent Owner and disclosed in the above-mentioned WO2007/002433 publication. Patent Owner also described PLX4720 in the above-mentioned (PNAS) article.

GSK published another article on February 2013 describing its development of the infringing dabrafenib compound and touting the importance of the core structure of the ’640 patent: “Having established the sulfonamide as a ***key pharmacophore required for potent cellular inhibition*** of BRaf^{V600E},” the authors explained, “we performed significant structural modifications elsewhere to lower the molecular weight and reduce the number of metabolic sites contained within the template.” Ex. 2006 at 1.

In addition to the core structure, the proper substituents needed to yield an overall shape and size that selectively inhibit BRAF^{V600E} kinases is also disclosed and claimed in the ’640 patent. This overall structure is reflected in every single

generic formula in the specification, *see* Ex. 1001 at formulae Ia-Ij, and is another identifying characteristic of the claimed invention.

As the foregoing shows, Patent Owner invented an important BRAF kinase inhibitor including the novel core structure consisting of a fluorinated phenyl with the fluorine adjacent to a sulfonamide coupled to six different substituents to yield molecules with a particular overall shape and size. Any argument that the core structure—which appears in 120 individual chemical compounds in the patent—and the overarching structure—which appears in multiple generic formulae in the patent—are not fundamental identifying characteristics is without merit.

d. Petitioner’s Written Description Argument Is Ultimately Based On Legal Error

Having adopted for its own use the core structures disclosed in the ’640 patent, Petitioner now seeks to avoid the ’640 patent by arguing that there is inadequate written description for two of the substituents within the disclosed structures. In particular, Petitioner points to L_1 and R^1 , and contends that the particular claimed combinations are inadequately described. Yet, a cursory review of Petitioner’s arguments shows that they ultimately boil down to an unduly narrow and legally erroneous understanding of the written description requirement.

Petitioner repeatedly argues that the alleged lack of examples involving L_1 as a bond and the claimed R^1 substituents shows that the written description requirement is not satisfied. *See, e.g.,* Petition at 30 (“none of the

examples...describes a compound where L_1 is a bond...."); *id.* at 31 (The “absence in P2 of any representative species where L_1 is a bond, would have suggested to a person of ordinary skill that as of the filing date of P2 the applicants did not possess the subgenera of the Challenged Claims.”); *id.* at 45 (“Although the Challenged Claims encompass trillions of compounds, P2 describes only three species that have an R^1 that is ‘optionally substituted lower alkyl’....”).

Petitioner, however, cites no legal support for its arguments that a particular number of representative species are required to satisfy the written description requirement. In fact, the law has long been clear that there is no such requirement. Rather, a “specification may, within the meaning of 35 U.S.C. § 112 ¶ 1, contain a written description of a broadly claimed invention without describing all species that claim encompasses.” *Utter*, 845 F.2d at 998-99.

The number of cases that have affirmed this principle over the years is overwhelming. *See, e.g., Cordis Corp. v. Medtronic AVE, Inc.*, 339 F.3d 1352, 1365 (Fed. Cir. 2003) (“As our case law makes clear...‘[a]n applicant is not required to describe in the specification every conceivable and possible future embodiment of his invention.’”) (citation omitted); *Pfizer Inc. v. Teva Pharm. USA, Inc.*, 555 F. App’x 961, 968 (Fed. Cir. 2014) (written description does not require inventors “to reduce to practice and be in physical possession of every species...of a genus...claim;” “an application satisfies the written description

requirement when it details ‘relevant identifying characteristics’ such that the compound can be distinguished from other compounds.”); *In re Angstadt*, 537 F.2d 498, 502–03 (C.C.P.A. 1976) (patentees “are not required to disclose every species encompassed by their claims even in an unpredictable art”) (quoted in *Regents of the Univ. of Cal.*, 119 F.3d at 1569); *In re Grimme*, 274 F.2d 949, 952 (C.C.P.A. 1960) (“[I]t has been consistently held that the naming of one member of such a group is not, in itself, a proper basis for a claim to the entire group. However, it may not be necessary to enumerate a plurality of species if a genus is sufficiently identified in an application by ‘other appropriate language.’”); *Pfizer*, 405 F. Supp. 2d at 505 (explaining that “generic formula description contained in the ’893 patent is sufficient to satisfy the written description requirement, regardless of whether the specific isomeric compounds are individually described in the patent”).

It is true that the challenged claims encompass a large number of compounds, not all of which are exemplified in the patent. But this is not surprising, nor is it indicative of a lack of written description. In fact, it makes sense that a patentee who has invented a novel and important chemical structure will claim variations of it without individually describing each of the many variations. If there were a requirement to disclose an example of every variation, patents to chemical compounds would become empty and meaningless, as accused

infringers—such as Petitioner—could easily evade them by making trivial chemical modifications to the disclosed exemplary species.

For this reason, a patentee “should not be denied the use of language necessary to give him the broadest protection commensurate with the scope of his disclosed invention.” *In re Grier*, 342 F.2d 120, 126 (C.C.P.A. 1965); *see also In re Angstadt*, 537 F.2d at 502–03 (noting that requiring disclosure of every species within a genus claim would require a prohibitive amount of experimental work of the patentee); *In re Fuetterer*, 319 F.2d 259, 265 (C.C.P.A. 1963) (Rich, J.) (disclosure of four species was sufficient even for huge genus that was not fully known at the time of the invention).

Here, Patent Owner invented a novel chemical structure for BRAF kinase inhibition. To use the written description requirement to invalidate the claims would be to deny Patent Owner the very language necessary to adequately protect its invention. *See, e.g., In re Driscoll*, 562 F.2d at 1249-50 (describing the “predicament” patentees would experience in seeking to adequately claim their invention if a disclosure of 14 chemical groups could not support a claim with only one group); *see also In re Johnson*, 558 F.2d 1008, 1019 (C.C.P.A. 1977) (only “a hypertechnical application of legalistic prose” could lead to the “notion that one who fully discloses, and teaches those skilled in the art how to make and use, a genus and numerous species therewithin, has somehow failed to disclose...that

genus minus two of those species”). Such a result is particularly unjustified here given the quality of the disclosure for the entirety of the claimed genera, as documented above. *See supra* Parts I.A.1.a, I.A.1.b.

Seemingly acknowledging the specification literally discloses the compounds recited in the claims, Petitioner further argues that the written description requirement is nonetheless violated because the specification does not sufficiently “focus” on these compounds or express a “preference” for them. The Petition is littered with such arguments. *See, e.g.*, Petition at 27 (“P2 does not guide one of ordinary skill to **focus** on either of these two options for L₁...”); *id.* at 29 (“The schemes included in P2 similarly do not support a **preference** for L₁ as ‘a bond or –N(H)C(O)–.’”); *id.* at 30 (“P2 does not provide a **preference** for a subgenus with this combination of L₁ groups or where L₁ is ‘a bond.’”); *id.* (“P2, viewed as a whole, does not direct one of ordinary skill to focus on these compounds or indicate a **preference** for these compounds....”); *id.* at 35 (“P2 does not guide one of ordinary skill to focus on any of these three options....”); *id.* at 39 (“Similarly, P2 does not set forth a **preference** for these specific R¹ groups, or a subgenus that is limited to these R¹ groups.”); *id.* at 39-40 (“The absence in P2 of any **preference** for the R¹ groups recited in the Challenged Claims...would have suggested to a person of ordinary skill that, as of the filing date of P2, the applicants did not possess the subgenera of the Challenged Claims.”).

All of these complaints about “focus” and “preference,” however, are legally irrelevant. Indeed, Petitioner cites no law suggesting that the specification must express a “preference” for a particularly claimed embodiment for the written description requirement to be satisfied. In fact, the law is to the contrary. As Judge Bryson has explained, “a patentee need not indicate that one embodiment is ‘of special interest’ in order to claim it.” Rather, “a patentee is free to selectively claim one particular embodiment without running afoul of the written description requirement.” *Erfindergemeinschaft UroPep GbR v. Eli Lilly & Co.*, 276 F. Supp. 3d 629, 656-57 (E.D. Tex. 2017) (Federal Circuit Judge Bryson presiding), *aff’d*, 2018 WL 4922997 (Fed. Cir. Oct. 10, 2018).

In sum, Petitioner’s written description arguments based on an alleged lack of examples or “focus” on particular embodiments are contrary to law and entitled to no weight.

2. Petitioner Fails To Show Lack Of Enablement Support For The Challenged Claims

In addition to its written description challenge, Petitioner presents two enablement arguments, neither of which are directed to the core structure of the claimed invention. Rather, both of Petitioner’s arguments focus on a single aspect of just one of the many substituents in the claimed compounds.

Specifically, while Petitioner acknowledges that the claimed compounds where L₁ is –N(H)C(O)– are properly enabled, Petitioner contends that compounds

where L_1 is a bond are not enabled. First, Petitioner contends that P2 does not enable a POSITA to make the full scope of claimed compounds for which L_1 is a bond. Petition at 41. Second, Petitioner contends that P2 does not enable a POSITA to use such compounds. *Id.*

Both of Petitioner's arguments fail for the reasons discussed below.

e. P2 Enables A POSITA To Make The Full Scope Of Claimed Compounds For Which L_1 Is A Bond

To prevail on its enablement challenge, Petitioner must demonstrate that a POSITA would not have been able to make or use the full scope of the claimed compounds without **undue** experimentation. The test for undue experimentation, however, is not merely whether experimentation is necessary; indeed, “a considerable amount of experimentation is permissible” as long as it is “merely routine” or the “specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.” *PPG Indus., Inc. v. Guardian Indus. Corp.*, 75 F.3d 1558, 1564 (Fed. Cir. 1996) (quotation and citation omitted).

Likewise, the “fact that experimentation may be complex...does not necessarily make it undue, if the art typically engages in such experimentation.” *See In re Certain Limited-Charge Cell Culture Microcarriers*, No. 337-TA-129, 1983 WL 54215, at *10 (I.T.C. Nov. 18, 1983), *aff'd. sub nom.*, *Massachusetts*

Institute of Technology v. A.B. Fortia, 774 F.2d 1104 (Fed. Cir. 1985). Petitioner does not come close to making the required showing under this high standard.

Petitioner cannot dispute that P2 discloses, in Example 2, a reaction scheme for synthesizing the claimed genera of compounds in which L₁ is a bond. As documented above, P2 describes and illustrates a Suzuki coupling for this very purpose. Petition at 44-45. Petitioner admits that Suzuki couplings are “widely used in the pharmaceutical industry,” and have been known in the art since 1978. *Id.* at 45.

In fact, this is a gross understatement. Given how versatile and useful the Suzuki reaction has proven to be, its inventors were awarded the 2010 Nobel Prize in chemistry. During the Suzuki Nobel Lecture, the reaction was noted for its “easy use of the reaction both under aqueous and heterogeneous conditions” and “toleration of a broad range of functional groups.” Ex. 1025 at 5-6.

Against this backdrop, Petitioner now strangely contends that the challenged claims are not enabled because it would require **undue** experimentation for a POSITA to make **some** of the claimed compounds where L₁ is a bond. In particular, Petitioner’s attacks focus on one sub-genus in which L₁ is a bond and Ar is a heteroaryl group, with some of Petitioner’s arguments directed even more narrowly only to instances where Ar is a five-membered, 2-heteroaromatic group such as thiazole. Such arguments are without merit.

To try and meet its burden of showing a need for undue experimentation, Petitioner relies solely on a small set of cherry-picked publications with out-of-context soundbites that supposedly support its position. While Petitioner also cites its expert, Dr. Baran, Dr. Baran does nothing more than quote the cited articles with no further analysis or explanation.

Petitioner's articles reflect nothing more than the rapid development and expansion of a powerful chemical method as researchers quickly overcame routine issues to expand its application to new types of compounds. In fact, the very articles that Petitioner relies upon soundly demonstrate that at the time P2 was filed in 2008, Suzuki couplings were widely recognized by POSITAs as "one of the most frequently employed Pd-catalyzed C-C bond-forming reactions," and "an important tool in medicinal chemistry as well as in the large-scale synthesis of pharmaceuticals and fine chemicals." *See* Ex. 1026 at 6; Ex. 1018 at 2.

Likewise, Petitioner's articles recognize the Suzuki coupling as "one of the most efficient methods for the construction of biaryl or substituted aromatic moieties" and a highly flexible reaction mechanism, with key advantages including "the mild conditions under which it is conducted, the high tolerance toward functional groups that is observed, the commercial availability and stability of boronic acids to heat, oxygen, and water, and the ease of handling and separation of boron-containing byproducts from the reaction mixtures." Ex. 1018 at 1-2; *see*

also Ex. 1025 at 5-6 (“easy use of the reaction both under aqueous and heterogeneous conditions” and “toleration of a broad range of functional groups” are advantages of the Suzuki coupling).

Petitioner’s references further demonstrate the extensive scope of experimentation that was routine in this area of the art, including synthesis experiments to develop a wide variety of reactants and catalysts and to test new applications of the Suzuki coupling under varied reaction conditions. *See, e.g.*, Ex. 1022 (synthesis of boronic acids), Ex. 1018 (historical account of experiments to test and optimize dialkylbarylphosphine ligands for Suzuki couplings).

Even though these publications demonstrate that no undue experimentation would be required in view of the description of the patents-in-suit, Petitioner nevertheless advances several alleged justifications for its argument that L₁ as a bond is not enabled. As documented below, however, Petitioner’s own evidence simply confirms that the materials and reactions necessary to make the claimed compounds were well within the knowledge of the POSITA.

(1) Petitioner Has Not Shown That Suzuki Couplings Involving 5- Or 6-Member Heteroaryls Are Not Enabled

First, Petitioner argues that boronic acids of formula 11 in which the Ar group is a 5- or 6-member heteroaryl wherein at least one atom is nitrogen “remain difficult or impossible to use in Suzuki reactions even to this day.” Petition at 45-

46. Petitioner cites Dr. Baran in support. The cited paragraph of Dr. Baran's declaration, however, merely parrots word-for-word the corresponding paragraph in the Petition, with no citation to any publication or other prior art to substantiate the assertion. Such conclusory expert testimony that simply tracks and repeats the arguments in the Petition is entitled to little or no weight. 37 C.F.R. § 42.65(a); *Wowza Media Sys., LLC v. Adobe Sys., Inc.*, IPR2013-00054, Paper 16 at p. 4 (P.T.A.B. Jul. 13, 2013).

Petitioner next asserts, again citing Dr. Baran, that Suzuki couplings with heteroaryl reactants had "proven significantly more challenging than those with all-carbon reactants (e.g., an aryl)" as of 2008. Petition at 46. While the Martin paper cited by Dr. Baran includes this general observation, it goes on to explain how to overcome such challenges: "use of XPhos (L8) as supporting ligand allowed an expansion of the scope of the SMC [Suzuki-Miyaura coupling] for the combination of thiophene and pyridylboronic acids with a wide range of activated and unactivated heteroaryl chlorides, even highly basic aminopyridines, with high efficiency and relatively low catalyst loadings." See Ex. 1018 at 6-7. The use of such supporting ligands was known to POSITAs and published in 2007, prior to the filing of P2. See *id.* at 13 (endnote 39). Thus, far from supporting Petitioner's non-enablement argument, Martin confirms that a POSITA would have been able

to carry out Suzuki couplings with heteroaryl reactants without undue experimentation.

Petitioner also claims that “many standard protocols for Suzuki reactions fail in the presence of reactants bearing a free-NH group,” citing Dr. Baran and Dufert. But Dufert expressly cites two 2008 papers regarding the use of S-Phos as a supporting catalyst as providing a “general exception” to this claim. *See* Petition at 46; Ex. 1019 at 1, 7 (endnote 4). Thus, as evidenced by the “general exception” papers cited in Dufert, it was known to POSITAs in 2008 that the purported failure of Suzuki reactions involving reactants with a free-NH group could be overcome by using S-Phos as a supporting catalyst. Rather than supporting Petitioner’s position, Dufert thus again confirms that such Suzuki couplings were enabled.

Petitioner and Dr. Baran further assert, citing Martin, that steric hindrance due to two *ortho* ligands in each reactants required to form the claimed compounds would have inhibited the Suzuki cross-coupling. *See* Petition at 46-47. But Martin itself discloses that cross-coupling sterically hindered reactants possessing two *ortho* substituents had been achieved using either a phenanthrene derivative L6, or SPhos. *See* Ex. 1018 at 4 (“Our initial efforts utilized phenanthrene derivative L6, which proved to be an excellent ligand for the construction of tetra-*ortho*-substituted biaryls via SMC. We later found that SPhos (L7), which can be prepared in an experimentally convenient one-pot protocol from 1,3-

dimethoxybenzene, was an outstanding ligand for this and other purposes.”); *see also id.* at Abstract (“With the use of such dialkylbiarylphosphine ligands, the coupling of unactivated aryl chlorides, aryl tosylates, heteroaryl systems, and very hindered substrate combinations have become routine.”). The papers cited by Martin disclosing these solutions were published in 2002 and 2004-2005, respectively. *Id.* at 13 (endnotes 27, 28). Thus, solutions to each of these purported “problems” were already well known to POSITAs in 2008 when P2 was filed, and a POSITA would have been able to employ these solutions without undue experimentation.

(2) Petitioner Has Not Shown That Suzuki Couplings With Five-Membered, 2-Heteroaromatic Boronic And Pyridinyl Boronic Acids Are Not Enabled

Petitioner next asserts that the claimed compounds include those that require “a cross-coupling involving a five-membered, 2-heteroaromatic boronic acid or pyridinyl boronic acid” and that such reactants “were unstable, and substantial efforts were required to identify unique palladium catalyst(s) for the Suzuki reaction to occur.” Petition at 47. Dr. Baran’s declaration copies the Petition verbatim, and cites generally to an article by Kinzel. Ex. 1002 at ¶ 116.

Kinzel, however, does not disclose that *all* five-membered, 2-heteroaromatic boronic acids are unstable; rather, Kinzel identifies Suzuki couplings of eight particular boronic acids—“the SMCs of quickly deboronating 2,6-

difluorophenylboronic acid (1) and analog 2 as well as the SMCs of five-membered 2-heterocyclic boronic acids 3-8”—that it characterizes as “problematic.” Ex. 1020 at 1.

Further, even with respect to these eight compounds, Kinzel states that a “viable solution” to their tendency to deboronate was already known: “the masking of the boronic acids as MIDA boronates, cyclic triolborates, or trifluoroborate salts, which slowly hydrolyze to the free boronic acid under the reaction conditions.” *Id.* The articles cited by Kinzel for the cyclic triolborate and trifluoroborate salt approaches show that these solutions were published in 2008 and 2003, respectively, and therefore would have been known to a POSITA at the time that P2 was filed. *Id.* at 3 (endnotes 8 and 9). Thus, Kinzel’s teachings are again contrary to Petitioner’s non-enablement arguments, and actually support a finding that the challenged claims were enabled.

Petitioner and Dr. Baran also cite Jedinak for the proposition that “2-heteroaryl and pyridinyl boronic acids remained problematic with respect to Suzuki couplings because of their instability and/or poor reactivity leading to undesired side reactions such as protodeboronation and oxidative coupling.” Petition at 47. Petitioner, however, neglects to disclose that Jedinak goes on to state that “the development of alternative organoboron reagents, particularly MIDA esters and trifluoroborates, solved” this issue. Ex. 1021 at 1. The paper

cited by Jedinak for the trifluoroborate solution was published in 2007, and therefore would have been known to POSITAs when P2 was filed. *Id.* at 13 (endnote 20). Yet again, Petitioner’s own evidence undermines any contention that undue experimentation would have been required to obtain suitable starting materials to make the claimed compounds by Suzuki coupling.

Petitioner and Dr. Baran, citing Tyrell, also contend that “it was exceedingly difficult – if not impossible – to obtain the boronic acid starting materials that were required to make the compounds of the Challenged Claims,” and that “[t]he disclosure in P2 does not teach a POSITA how to obtain the requisite boronic acid starting materials.” Petition at 47. This criticism, however, ignores the aforementioned disclosures of Kinzel, Jedinak, and the papers cited therein that the corresponding esters, triolborates, and trifluoroborates of these boronic acid materials could be used in Suzuki couplings to obtain the same resulting compounds. As noted above, the use of these alternatives was disclosed and well known in the art by the time P2 was filed in 2008. Petitioner and Dr. Baran do not contend that these alternative materials would have been difficult to obtain. The Petition is silent in all respects as to these materials.

Moreover, the Tyrell paper cited by Petitioner—which was published in 2002, well before the filing of P2—further discloses that for heterocyclic boronic acids that were too difficult to synthesize, “the corresponding haloderivative can

act as the electrophilic coupling partner in the Suzuki coupling reaction.” Ex. 1022 at 13. In other words, Tyrell teaches that in 2002, it was known that the same result could be obtained from a Suzuki coupling by introducing the heterocyclic component via the halide, rather than the boronic acid. Petitioner also does not contend that these corresponding haloderivatives were difficult to obtain. Finally, the Martin article that was previously cited by Petitioner expressly discloses, citing a 2005 publication, that one of the advantages of the Suzuki coupling is “the commercial availability” of boronic acids. Ex. 1018 at 2, 12 (endnote 5). All of these references undercut Petitioner’s enablement arguments by demonstrating that it was known how to obtain suitable starting materials for the Suzuki couplings necessary to form the claimed compounds.

(3) Petitioner Has Not Shown That Undue Experimentation Was Required To Procure The Necessary Boronic Acid Reagents

Petitioner further asserts that “the stability of boronic acid reagents like compound 11 varies widely and is highly unpredictable, and many such boronic acid reagents are, therefore, unstable and cannot be used, even if they could be made.” Petition at 47-48. According to Petitioner, this “requires the POSITA to synthesize millions if not trillions of boronic acids from scratch in order to make the full scope of the claimed genera.” *Id.* at 48. Petitioner again asserts that only “a very small subset of the boronic acids necessary to make the full scope of the

Challenged Claims were commercially available during the relevant time period,” and that substituted 5 or 6-membered heteroaryl boronic acids “were not commercially available.” *Id.*

None of these assertions, however, is supported by **any** record evidence. The Petition cites none, and Dr. Baran’s declaration simply repeats the Petition, almost entirely verbatim, without citation to any supporting evidence. Such unsupported testimony is entitled to little or no weight. Petitioner’s failure to support its position with underlying facts or data is particularly telling in light of Martin’s disclosure, discussed above, that it has been known since at least 2005 that one of the advantages of the Suzuki coupling is “the commercial availability” of boronic acids. Ex. 1018 at 2, 12 (endnote 5).

Additionally, even if Petitioner’s contentions were credibly supported by record evidence, Petitioner nonetheless ignores the evidence discussed above that the corresponding esters, triolborates, trifluoroborates, and/or haloderivatives could be used in place of the boronic acids in Suzuki couplings to generate the same compounds. Ex. 1020 at 1; Ex. 1021 at 1; Ex. 1022 at 13. As noted above, Petitioner has not asserted that the corresponding esters, triolborates, trifluoroborates, and haloderivatives of the necessary boronic acids could not be readily obtained, either commercially or through synthesis. Nor does Petitioner

contend that a POSITA would not have been able to utilize these alternative materials in a Suzuki coupling without undue experimentation.

(4) Petitioner Has Not Shown That Undue Experimentation Would Have Been Required To Optimize The Suzuki Coupling To Produce The Claimed Compounds.

Petitioner next asserts that “performance of the Suzuki reaction step itself would have been highly unpredictable.” Petition at 48-49. Petitioner argues, for example, that “4-thiazolyl boronic acids are well-documented to fail in Suzuki reactions” because they “are very unstable and are subject to a phenomenon called protodeboronation,” citing Dr. Baran, Hammerle, and Cox. *Id.* at 49. Consistent with Kinzel, Jedinak, and Tyrell, however, Hammerle goes on to teach the solution to this problem, namely, using derivatives of the boronic acid such as boronic esters (Hammerle’s compounds 5 and 9) and/or haloderivatives (Hammerle’s compounds 2, 3, 6, and 7). *See* Ex. 1023 at 2 (*e.g.*, “In order to perform Suzuki-Miyaura reactions we prepared thiazoleboronic esters 5 and 9 since the corresponding acids turned out to be unstable in our hands.”). As discussed above, Petitioner does not address these alternative reactants, nor provide any evidence that a POSITA would not have been able to use them in Suzuki couplings without undue experimentation.

Petitioner further notes that the success or failure of the Suzuki coupling “depends on the identity and nature of compounds 10 and 11, the base, the catalyst,

and the solvent used,” citing the Suzuki Nobel Lecture and Li. Petition at 49. From this, Petitioner concludes that the Suzuki coupling is “unpredictable” and “highly sensitive to reaction conditions.” *Id.*

While the cited references certainly state that reaction conditions make a difference, they do not support Petitioner’s conclusion that the reaction is “unpredictable” or “highly sensitive.” The Suzuki Nobel Lecture, for example, expressly notes that “easy use of the reaction both under aqueous and heterogeneous conditions” and “toleration of a broad range of functional groups” are well-known advantages of the Suzuki coupling. Ex. 1025 at 5-6.

Moreover, although the Suzuki Nobel Lecture identifies the requirement for a base as a potential “defect” of the reaction, it discloses that this can be readily overcome “by using suitable solvent systems and adequate bases.” *Id.* at 6; *see also* Ex. 1026 at 6-7 (noting that the limitations of organoboronic acids “are usually not insurmountable obstacles and problems can frequently be solved with a judicious choice of reaction conditions”). The fact that some selection and optimization of reaction conditions may be necessary in order to synthesize the claimed compounds by Suzuki coupling does not indicate that such synthesis is not enabled. Experimentation that is merely routine, even if a considerable amount, is not undue, even if optimization of a given composition may require adjustment of a large number of variables. *Alcon Research Ltd. v. Barr Labs., Inc.*, 745 F.3d

1180, 1189 (Fed. Cir. 2014); *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). Petitioner has advanced no evidence showing that optimization of the Suzuki coupling in this case is anything other than routine.

Petitioner also contends that “P2 does not teach that the 1978 reaction conditions set forth in Step 4 would work to perform the Suzuki reaction to obtain the claimed compounds.” Petition at 50-51. Petitioner contends, for example, that the palladium catalyst and potassium carbonate base would not work in a Suzuki coupling involving heteroaryl reactants. *Id.* Petitioner further asserts that “[e]ven using newer, more sophisticated catalysts that were developed after the disclosure in P2, such reactions would be very difficult.” *Id.*

But Petitioner’s contentions in this regard are unsupported by any factual evidence of record. Petitioner cites to paragraphs 123-126 of Dr. Baran’s declaration, which simply copy, verbatim, the corresponding paragraphs in the Petition with no citation to any supporting evidence or data. This *ipse dixit* of Petitioner’s expert is entitled to little or no weight because it fails to disclose the underlying facts or data upon which it is based.

Moreover, Petitioner’s attack on the original 1978 Suzuki coupling conditions is misplaced, because the test for enablement is not merely whether a POSITA could make or use the invention from the disclosures in the specification; it is whether a POSITA could make or use the invention by coupling those

disclosures with information known in the art. *United States v. Telectronics, Inc.*, 857 F.2d 778, 785 (Fed. Cir. 1988). The disclosure itself need not teach, and preferably omits, that which was already known in the art. *In re Buchner*, 929 F.2d 660, 661 (Fed. Cir. 1991). Thus, Petitioner's attack on the original 1978 conditions for the Suzuki coupling is inapposite, because as has been discussed above, the Suzuki coupling was a well-known reaction in 2008 that was used by POSITAs in a wide variety of applications. Ex. 1026 at 6; Ex. 1018 at 2.

Further, the record shows that because of this widespread application, many variations of starting reactants, catalysts, bases, and solvents were known in the art and within the skill of a POSITA when P2 was filed in 2008, including, for example, the triolborates, trifluoroborates, and haloderivatives of boronic acids discussed in Kinzel, Jedinak, and Tyrell, and the X-Phos and S-Phos supporting catalysts discussed in Martin and Dufert. *See, e.g.*, Ex. 1020 at 1; Ex. 1021 at 1; Ex. 1022 at 13; Ex. 1018 at 4, 6-7; Ex. 1019 at 1, 7 (endnote 4).

Aside from the conclusory, unsupported contention in Dr. Baran's declaration that Suzuki couplings using newer, more sophisticated catalysts would nonetheless have been "very difficult," Petitioner cites no evidence whatsoever suggesting that a POSITA could not have adapted these and other components to perform the necessary Suzuki couplings with the routine exercise of ordinary skill. The fact that it was routine in the art to publish the reaction conditions for different

variations of the Suzuki coupling in technical journals and articles, as evidenced by the very papers and articles cited by Petitioner, suggests that POSITAs would have been able to look up the necessary combination of conditions for a given synthesis and optimize them for a particular application with no more than routine experimentation.

Petitioner and Dr. Baran purport to examine an “illustrative example” involving the synthesis of dabrafenib and similar compounds using a Suzuki coupling. Petition at 51-53. In doing so, Petitioner and Dr. Baran simply repeat and restate the arguments already discussed above.⁹ These arguments fail for the reasons set forth above.

⁹ Petitioner additionally concludes that because GSK did not use Suzuki coupling to synthesize dabrafenib, the reaction must be impossible to perform. Petition at 51. This conclusory assertion is supported by no evidence from any credible witness or declarant with knowledge of GSK’s motivations, and should be given no weight.

**(5) The Wands Factors Support A Finding That
The Challenged Claims Are Enabled By P2**

Petitioner concludes by purportedly applying the *Wands* factors to its arguments to support a finding of non-enablement. If anything, however, the evidence relating to each of the *Wands* factors confirms that the challenged claims are enabled:

- **1. The quantity of experimentation necessary.** As discussed above, Petitioner's own references demonstrate the extensive scope of experimentation that was routine in this area of the art, including synthesis experiments to develop reactants and catalysts and to test new applications of the Suzuki coupling under varied reaction conditions. *See, e.g.*, Ex. 1022 (synthesis of boronic acids), Ex. 1018 (historical account of experiments to test and optimize dialkylbarylphosphine ligands for Suzuki couplings).
- **2. The amount of direction or guidance presented.** As discussed above, widespread applications and variations of the Suzuki coupling were known in the art as of 2008, and the publication of these different applications and variations provided significant guidance to a POSITA on how to apply the Suzuki coupling to link

different types of compounds and functional groups. *See, e.g.*, Ex. 1020, Ex. 1021, Ex. 1022.

- **3. The presence or absence of working examples.** As noted, P2 includes an express disclosure of the Suzuki reaction protocol. Likewise, the state of the art in 2008 included widespread publication of different applications and variations of the Suzuki coupling, providing countless working examples to a POSITA.
- **4. The nature of the invention.** The challenged claims pertain to a genus of compounds that all have the core structure of a fluorinated phenyl bonded to a sulfonamide. Reaction mechanisms, such as the Suzuki coupling, for further linking this core structure to an optionally substituted heteroaryl, as required by the claims, were well known. *See, e.g.*, Ex. 1026 at 6; Ex. 1018 at 2. Thus, the nature of the claimed invention is such that a POSITA could have made the claimed compounds without undue experimentation.
- **5. The state of the prior art.** As discussed for Factors 2 through 4, different variations and applications of the Suzuki coupling were known to a POSITA in 2008, thus enabling a POSITA to use the

Suzuki coupling to link a variety of different structures with only routine experimentation and optimization.

- **6. The level of skill in the art.** Petitioner admits that this is high. Petition at 56. It is thus undisputed that this supports a finding of enablement.
- **7. The predictability of the art.** As discussed for Factors 2-5, many variations of the Suzuki coupling were known to a POSITA in 2008, thus allowing a POSITA to reasonably predict, with only routine experimentation and optimization, how best to optimize a Suzuki coupling to make a compound within the scope of the challenged claims.
- **8. The breadth of the claims.** Although the claims cover a large number of compounds, this breadth is commensurate with the aggregate disclosure in P2 and the prior art, in which the Suzuki coupling and many of its applications and variations were well known as of 2008.

Thus, P2's disclosure enables a POSITA to make the claimed compounds.

f. P2 Enables A POSITA To Use The Full Scope Of Claimed Compounds For Which L₁ Is A Bond

At the end of its Petition, Petitioner presents a passing argument that P2 does not enable a POSITA to use the full scope of claimed compounds for which L₁ is a bond. Petitioner's contention turns on the incorporation of § 101's utility requirement into the "how-to-use" prong of the enablement requirement, because Petitioner simply argues that P2 does not disclose that claimed compounds in which L₁ is a bond have the claimed utility of modulating protein kinases. See Petition at 56-61.

Thus, as an initial matter, Petitioner's "how-to-use" argument is merely a § 101 argument disguised as an IPR. As discussed in Part III.A, this is an improper end-run around the statutory requirement that IPRs be based upon patents or printed publications.

Petitioner's argument also fails because the Federal Circuit has "rejected enablement challenges based on the theory that there can be no guarantee that prophetic examples actually work." *Alcon Research Ltd. v. Barr Labs., Inc.*, 745 F.3d 1180, 1189 (Fed. Cir. 2014). Rather than "showing that any particular" claimed compound modulates protein kinases, P2 needs only enable a POSITA to practice the invention of using a claimed compound to modulate protein kinases. See *Erfindergemeinschaft*, 276 F. Supp. 3d at 662. As discussed below, P2 meets this standard.

P2 discloses the following utility for *all* of the compounds that fall within Formula I:

“The present invention concerns ***compounds of Formula I, and all sub-generic formulae***, that are modulators of protein kinases, for example without limitation, ***the compounds are modulators of at least one of the kinases*** selected from the group consisting of...”

Ex. 1004 at [0109]; *see also id.* at [0002] (“Compounds are contemplated that are active on protein kinases in general...”). Additionally, Petitioner admits that P2 includes tables with representative compounds that exhibit the claimed kinase modulating utility. Petition at 57. These tables include the compounds’ IC₅₀ activity data toward specific kinases, which as indicated in P2 are less than or equal to 10μM for the listed compounds. Ex. 1004 at 110-112 (Tables 2a-2p), [0234]-[0235].

Thus, P2 discloses a utility for all compounds falling within Formula 1, and further discloses representative assay results substantiating this utility. This is more than sufficient to support the requisite utility under §§ 101 and 112. *See, e.g., In re Gardner*, 475 F.2d 1389, 1392 (C.C.P.A. 1973), *reh’g denied*, 480 F.2d 879 (C.C.P.A. 1973) (finding that utility for a genus was supported through a showing of utility for one species).

Citing *In re Fouche*, 439 F.2d 1237, 1242-43 (C.C.P.A. 1971), Petitioner asserts that showing utility for only part of a genus is not sufficient to meet the

utility requirement, because the tables in P2 do not include any compounds where L_1 is a bond. Petition at 43, 57. As Petitioner concedes, however, *Fouche*'s holding only applies where a POSITA would not reasonably believe the entire genus would have the stated utility based on the limited disclosure. This is not the case here.

This case is most analogous to *In re Gardner*, which expressly distinguished *Fouche*. In *Gardner*, the claims-at-issue were directed to compounds with antihypertensive activity. The specification described the “generic group of compounds” as being “characterized by having the basic guanidinoalkyl-1,4-benzodioxan nucleus which imparts antihypertensive activity to such compounds.” *Gardner*, 475 F.2d at 1391. The specification also described a specific dosage – 5-25mg/kg – for “[t]he compounds of this generic invention.” *Id.* Although the specification described different compounds within the generic class as having varying levels of quantitative activity, the CCPA found that utility for the entire genus was sufficiently disclosed and that “[a] zero level of antihypertensive effectiveness is neither realistic nor consistent with the rest of the disclosure, considering particularly the specific dosages described for the compounds in general at the beginning of the specification.” *Id.* at 1392.

Here, as in *Gardner*, P2 discloses a utility—modulation of protein kinases—for the entire generic class of compounds falling within Formula 1. Ex. 1004 at

[0109]. Also as in *Gardner*, P2 discloses particular dosages – “0.01 to 50 mg/kg, also about 0.1 to 20 mg/kg of the subject being treated” – that are applicable “generally” to all of the claimed compounds. *Id.* at [0148]. In view of the description of utility, the disclosure of “specific dosages described for the compounds in general,” and the disclosure of several pages of exemplary compounds and their corresponding activity levels against specific kinases, a POSITA would have reasonably believed that the entire genus would have the stated utility. *Gardner*, 475 F.2d at 1392. Thus, as in *Gardner*, “the only reasonable interpretation” of the disclosure is “that all of the compounds possess each of the aforementioned activities, although in varying degrees.” *Id.*

In addition, the structural similarity of compounds in which L₁ is a bond to the compounds disclosed in Tables 2a-2p of P2 further support the utility of the claimed genus. As discussed in Part I.A.1.b, **all** of the compounds within the scope of Formula Ia have as a key “blaze mark” the core structure of a fluorinated phenyl bonded to a sulfonamide. This similarity would have provided a POSITA with additional reason to believe that all of the compounds within the scope of Formula Ia have, to some degree, the same kinase modulation utility as the compounds listed in Tables 2a-2p. This would have been further confirmed by publications in the art prior to July 16, 2008, disclosing that PLX4720, a compound featuring a sulfonamide group attached to a fluorinated phenyl group with the sulfonamide

adjacent to the fluorine, exhibiting targeted binding to the kinase BRAF V600E due to the interaction of the sulfonamide moiety with the BRAF V600E kinase. Ex. 2004.

Petitioner posits several reasons why a POSITA might believe that replacing an amide linker with a bond would lead to a lack of the disclosed utility. Petition at 57-60. None of these reasons, however, is supported by any credible evidence. Petitioner relies solely on Dr. Baran's declaration to support its assertions, which does nothing more than repeat the assertions made in the Petition, verbatim. "Expert testimony that does not disclose the underlying facts or data on which the opinion is based is entitled to little or no weight." 37 C.F.R. § 42.65(a); *Wowza Media Sys.*, IPR2013-00054, Paper 16 at 4. Thus, the Petition is supported by nothing more than attorney argument and Dr. Baran's *ipse dixit*. Having failed to put forth credible evidence to rebut the utility disclosed in P2, Petitioner cannot meet its burden of proving that P2 does not enable a POSITA to use the full scope of the claims.

IV. CONCLUSION

For the foregoing reasons, the Board should not institute review.

Dated: October 18, 2018

Respectfully submitted,

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CERTIFICATE OF COMPLIANCE

1. The undersigned certifies that this brief complies with the type volume limitations of 37 CFR § 42.24(a)(1)(i). This brief contains 13,960 words (excluding the table of contents, the table of authorities, mandatory notices under 37 CFR § 42.8, the certificate of service, certificate of compliance, and appendix of exhibits), as calculated by the “Word Count” feature of Microsoft Word 2016, the word processing program used to create it.

2. The undersigned further certifies that this brief complies with the typeface requirements of 37 CFR § 42.6(a)(2)(ii) and typestyle requirements of 37 CFR § 42.6(a)(2)(iii). This brief has been prepared in a proportionally spaced typeface using Microsoft Word 2016 in Times New Roman 14 point font.

Dated: October 18, 2018

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CERTIFICATE OF SERVICE

The undersigned hereby certifies that on October 18, 2018, a copy of the foregoing **PRELIMINARY RESPONSE TO PETITION FOR INTER PARTES REVIEW OF U.S. PATENT NO. 9,469,640** pursuant to 37 CFR § 42.107 was served via electronic mail upon the following:

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