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Paper 9
Entered: February 8, 2017

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

FUSTIBAL LLC,
Petitioner,

v.

BAYER HEALTHCARE LLC,
Patent Owner.

Case IPR2016-01490
Patent 8,637,553 B2

Before LORA M. GREEN, RAMA G. ELLURU, and ROBERT A. POLLOCK, *Administrative Patent Judges*.

POLLOCK, *Administrative Patent Judge*.

DECISION
Denying Institution of *Inter Partes* Review
37 C.F.R. § 42.108

I. INTRODUCTION

Fustibal LLC. ("Petitioner") filed a Petition requesting an *inter partes* review of claims 1–16 of U.S. Patent No. 8,637,553 B2 (Ex. 1001, "the '553 Patent"). Paper 1 ("Pet."). Bayer Healthcare LLC ("Patent Owner") filed a Preliminary Response to the Petition. Paper 6 ("Prelim. Resp."). We have jurisdiction under 35 U.S.C. § 6 and 35 C.F.R. § 42.4(a).

Institution of an *inter partes* review is authorized by statute when "the information presented in the petition . . . and any response . . . shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314; *see* 37 C.F.R. §§ 42.4, 42.108. Upon considering the Petition and the Preliminary Response, we exercise our discretion under 35 U.S.C. § 325(d) to decline Petitioner's request for institution of an *inter partes* review based on some grounds. In addition, we determine that Petitioner has not shown a reasonable likelihood that it would prevail in showing the unpatentability of any of the challenged claims. Accordingly, we decline to institute an *inter partes* review of claims 1–16 of the '530 Patent.

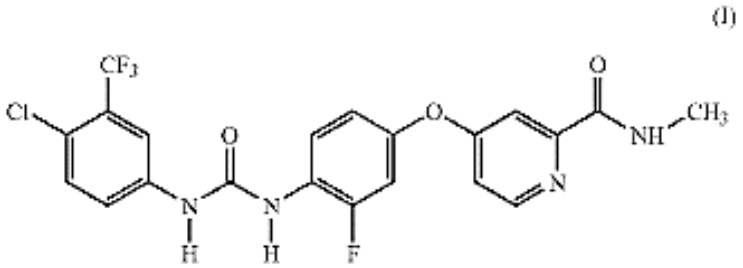
A. Related Applications and Proceedings

The '553 Patent to Boyer et al., issued from Application No. 10/895,985 ("the '985 Application"), filed July 22, 2004, and claims benefit of priority to Provisional Applications No. 60/489,102 and 60/540,326 filed July 23, 2003 and Feb. 2, 2004, respectively. Ex. 1001, [21], [60]. Patent Owner identifies a continuation application of the '985 Application, Application No. 13/669,103, as pending. *See* Paper 3, 2.

Patent Owner states that the '553 Patent has been asserted in the following district court proceedings: *Bayer HealthCare LLC v. Teva Pharm. USA, Inc.*, No. 1:16-01221-LPS (D. Del.) and *Bayer HealthCare LLC v. Apotex, Inc.*, No. 1:16-01222-LPS (D. Del.). Paper 8, 2. According to Petitioner, "the development of regorafenib (the claimed compound of the '553 Patent)" is at issue in *Onyx Pharms. Inc. v. Bayer Corp.*, Case No. C 09-2145 (EMC) (N.D. Cal. Oct 17, 2011). Pet. 1–2; *see* Prelim. Resp. 9–10 & n.4.

B. The '553 Patent and Relevant Background

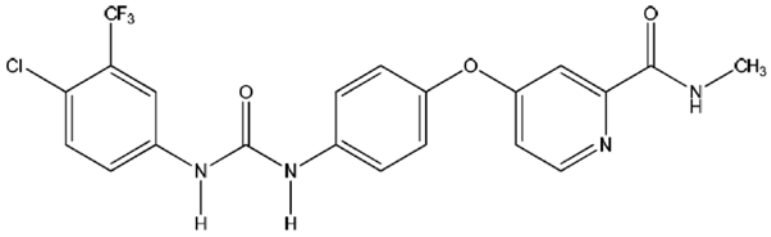
The '553 Patent is generally directed to "[a] compound of Formula I (reproduced below): salts thereof, prodrugs thereof, metabolites thereof, [and] pharmaceutical compositions containing such a compound." Ex. 1001, Abstract.



Formula 1 depicts the compound regorafenib, to which the '553 Patent is directed. The Specification describes compounds of Formula I as "potent inhibitor[s of] raf kinase, VEGFR kinase, p38 kinase, and PDGFR kinase, which are all molecular targets of interest for the treatment and prevention of osteoporosis, inflammatory disorders, hyper-proliferative disorders, and angiogenesis disorders, including cancer." *Id*. at 9:10–17.

The compound of Formula I (regorafenib), is the active ingredient in the anti-cancer drug STIVARGA®, marketed by Bayer HealthCare Pharmaceuticals Inc. for the treatment of certain types of colorectal cancer. *See* Pet. 4, Prelim. Resp. 1, 5; Ex. 2001,[1] 1, 11. Patent Owner points out that the discovery of regorafenib was preceded by the kinase inhibitor sorafenib, which has the following structure.

[1] STIVARGA® prescribing information dated June 2016.

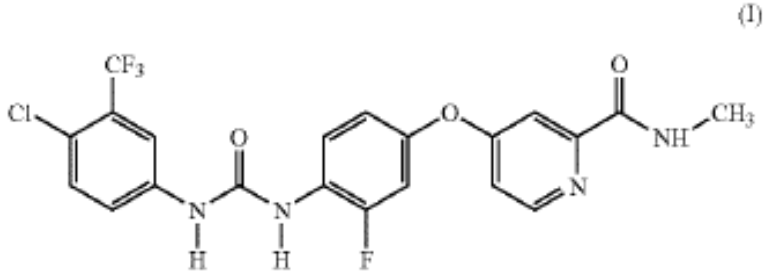


The above structure depicts the structure of sorafenib. Sorafenib is the active ingredient in the drug product NEXAVAR®, indicated for the treatment of certain renal, hepatocellular, and thyroid cancers. Prelim. Resp. 5; Ex. 2004[2], 1, 16; *see* Pet. 5.

C. Challenged Claims

Representative claim 13 recites:

13. A compound of Formula (I)



The remaining claims relate to salts, stereoisomers, and metabolites of the above compound.

D. The Asserted Prior art and Grounds of Unpatentability

Petitioner asserts the following grounds of unpatentability (Pet. 4):

Ground	Reference(s)	Basis	Claims
1	Riedl[3]	§ 102	1–16
2	Riedl	§ 103	1–16

[2] NEXAVAR® prescribing information revised November 2013.
[3] Riedl et al., WO 00/42012 A1, published July 20, 2000.

Ground	Reference(s)	Basis	Claims
3	Riedl, Ahern,[4] and Park[5]	§ 103	1–16
4	Riedl and Park	§ 103	1–16
5	Aherne and Park	§ 103	1–16

Petitioner also relies on the Declaration of Brian Shoichet, Ph.D. ("Shoichet Declaration"). Ex. 1008. As an initial matter, Patent Owner contends that Dr. Shoichet's Declaration should be accorded no weight because it fails to either state that it is made under penalty of perjury pursuant to 28 U.S.C. § 1764 or contain the affirmation prescribed in 37 C.F.R. § 1.68. Prelim. Resp. 19–20, 33. Although we agree with Patent Owner that the Shoichet Declaration is facially defective, at this stage of the proceeding, we decline to give the Declaration "no weight" on that basis.

E. Prosecution History Leading to the Issuance of the '553 Patent

Applicants disclosed Riedl in an Information Disclosure Statement dated March 18, 2008. Ex. 2005, 193. In allowing the then-pending claims, the Examiner's Reasons for Allowance provided that:

> After a thorough search, the closest prior art, WO 00/42012 to Riedl, et al. was found to teach similar phenyl-urea derivatives as kinase inhibitors. However, the WO document fails to teach or render obvious the instant claimed compounds according to Formula (I), and does not fairly suggest their salts or pharmaceutical compositions.

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[4] Aherne et al., *Finding the needle in the haystack: why high-throughput screening is good for your health*, 4(4) BREAST CANCER RES. 148–154, © 2002 BioMed Central Ltd.

[5] Park et al., *Metabolism of Fluorine-Containing Drugs*, 41 ANN. REV. PHARMACOL. TOXICOL, 443–70, © 2001 Annual Reviews.

Ex. 2005, 352–353.

Applicants repeatedly requested continued examination under 37 C.F.R. § 1.114 to permit the submission of additional art (*see id*. at 396, 568; Ex. 2006, 854) and the amendment of the claims (Ex, 2006, 695–702). Following each such submission, the Examiner issued a Notice of Allowability repeating the above-quoted Reasons for Allowance (Ex. 2005, 397, 569; Ex. 2006, 855), including with respect to claims 1–16 as issued (Ex. 2006, 913).

II. ANALYSIS

A. Person of Ordinary Skill in the Art.

Petitioner contends that a person of ordinary skill in the art "typically would have a PhD, MD, MS, or another degree relating to pharmaceutical chemistry (*e.g*. biology, chemistry, medicinal chemistry, medicine, pharmacology, or a closely related discipline), and . . . would have substantial familiarity, training, or experience with pharmaceutical compositions." Pet. 6. Patent Owner has not challenged Petitioner's proposed interpretation of a skilled artisan. We adopt Petitioner's proposed interpretation for purposes of this opinion. *See* Prelim. Resp. 6 & n.1; *see also Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (the level of ordinary skill in the art may be evident from the prior art).

B. Claim Construction

In an *inter partes* review, claim terms in an unexpired patent are interpreted according to their broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144–46 (2016) (upholding the use of the broadest reasonable interpretation standard).

Under that standard, we presume that a claim term carries its "ordinary and customary meaning," which "is the meaning the term would have to a person of ordinary skill in the art in question" at the time of the invention. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007); *see also Trivascular, Inc. v. Samuels*, 812 F.3d 1056, 1062 (Fed. Cir. 2016) ("Under a broadest reasonable interpretation, words of the claim must be given their plain meaning, unless such meaning is inconsistent with the specification and prosecution history."). Any special definition for a claim term must be set forth in the specification with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

Petitioner (correctly) contends that the '553 Patent expressly defines the claim term "pharmaceutically acceptable salt" as "'a relatively non-toxic, inorganic or organic acid addition salt of a compound of the present invention.'" Pet. 7 (quoting Ex. 1001, 9:56–62). Patent Owner does not presently object to this definition. Based on the specification's express disclosure, we agree that the cited definition applies. *See* Prelim. Resp. 6 & n.2. The parties agree that all other terms should be accorded their ordinary and customary meaning. *Id*.; Pet. 6–7.

Our reviewing court counsels that only those terms that are in controversy need be construed, and only to the extent necessary to resolve the controversy. *See Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999). Accordingly, for purposes of this decision, we determine that no further construction is necessary.

C. Ground 1: Anticipation by Riedl (Ex. 1002)

Petitioner asserts that claims 1–16 are anticipated by Riedl. Pet. 13–19. Patent Owner disagrees. Prelim. Resp. 7–21.

i. Overview of Riedl

Riedl teaches that "[t]he $p21^{ras}$ oncogene is a major contributor to the development and progression of human solid cancers and is mutated in 30% of all human cancers." Ex. 1002, 1:19–20.[6] In these cancer cells, mutated ras protein "delivers constitutive growth signals to downstream effectors such as the enzyme raf kinase." *Id*. at 1:21–28. Normal growth of such cells can be restored by inhibiting the raf kinase signaling pathway. *Id*. at 1:30–2:7. Studies have shown that interfering with the raf kinase signaling pathway in ras-transformed cells (i.e., by deactivating raf kinase or by expression of dominant negative mutants of MEK (the substrate of raf kinase)) can restore normal growth. *Id*.

Accordingly, Riedl discloses a class of compounds of the general Formula 1, purported to be "inhibitors of the enzyme raf kinase . . . useful . . . in the treatment of tumors and/or cancerous cell growth mediated by raf kinase." *Id*. at 2:10–20. Riedl presents no enzymatic or biological data for any individual compound.

The compounds of Formula 1 have the general structure A-D-B, where

> D is NH-C(O)-NH-,
>
> A is a substituted moiety of up to 40 carbon atoms of the formula: –-L-(M-L1)q , where L is a 5 or 6 membered cyclic structure bound directly to D, L^1 comprises a substituted cyclic moiety having at least 5 members, M is a bridging group having at least one atom, q is an integer of from 1-3; and each cyclic structure of L and L^1 contains 0-4 members of the group consisting of nitrogen, oxygen and sulfur, and

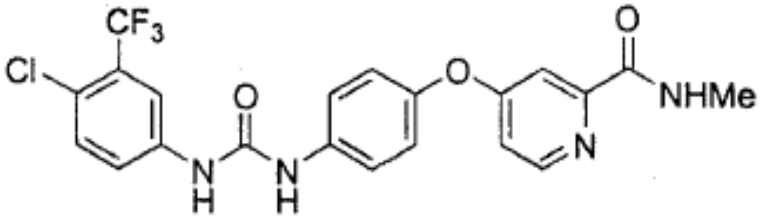
[6] We refer, herein, to the original pagination of the cited references rather than to that supplied by the parties.

> B is a substituted or unsubstituted, up to tricyclic aryl or heteroaryl moiety of up to 30 carbon atoms with at least one 6-member cyclic structure bound directly to D containing 0-4 members of the group consisting of nitrogen, oxygen and sulfur.

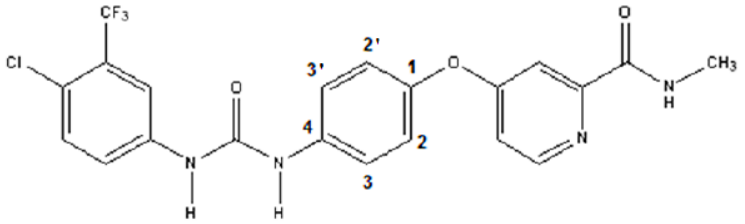
Id. at 2:22–3:8; *see also id* at 3:9–5:31 (further defining elements A and B).

Riedl further discloses the use of halogen moieties in at least portions of Formula I element B. *See id*. at 3:6–4:25. "Suitable halogen groups include F, Cl, Br, and/or I, from one to per-substitution (i.e. all H atoms on a group replaced by a halogen atom) being possible where an alkyl group is substituted by halogen, mixed substitution of halogen atom types also being possible on a given moiety." *Id*. at 6:5–8.

Riedl discloses numerous examples with the scope of Formula 1 including the formula for sorafenib:[7]



(*see id*. at 41:21–42:1). The above structure depicts the structure of sorafenib. At page 8 of the Petition, Petitioner numbers the central ring of sorafenib, which we adopt for convenience as shown below:



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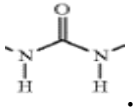
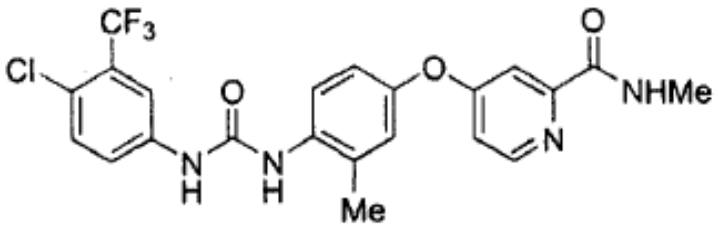
[7] For context, we note that "D" in the Formula 1 A-D-B structure is  .

See Ex. 1008 ¶ 50. The above structure depicts the structure of sorafenib with the carbons of the central ring numbered. Riedl also discloses the compound:



Id. at 43:1–4. The above structure is similar to sorafenib, but for a single substitution of methyl ("Me") for hydrogen at position 3 of the central ring. Elsewhere in the reference, Riedl presents the synthesis and structure of 103 "Exemplified Compounds" (*id*. at 53:15–88:5), including two compounds similar to sorafenib but for substitutions in the central ring of chlorine at position 3' (*id*. at 63:5–8, 81 (entry 49)), or chlorine at position 2' (*id*. at 63:21–26, 82 (entry 52)). *See* Ex. 1008 ¶ 51.

Relying on its expert, Dr. Shoichet, Petitioner contends that single halogen substitutions at position 3' or 2' of sorafenib provides the same molecule as single substitutions at position 3 or 2, respectively, such that Riedl inherently discloses single substitutions of chlorine at both the 3 and 2 positions of sorafenib. Pet. 15 (citing Ex. 1008 ¶¶ 51–54). Although Dr. Shoichet's explanation of this equivalency relies on exhibits not of record (*see* Ex. 1008 ¶¶ 52–53 (discussing Exhibits 1013 and 1014)), Patent Owner does not expressly deny the contention. *See e.g*. Prelim. Resp. 19 (arguing instead that "Dr. Shoichet's Declaration is not evidence and therefore is not properly before the Board at this time"). For purposes of this opinion only, we accept that Riedl discloses sorafenib, and examples structurally similar to sorafenib, with single substitutions of methyl at position 3, chlorine at position 3, and chlorine at position 2.

ii. Analysis of Ground 1 Under 35 U.S.C. § 325(d)

Institution of *inter partes* review is discretionary. *See* 35 U.S.C. § 314(a); 37 C.F.R. § 42.108. Our discretion on whether to institute is guided, in part, by 35 U.S.C. § 325(d), which states that "the Director may take into account whether, and reject the petition or request because, the same or substantially the same prior art or arguments previously were presented to the Office." Patent Owner requests that the Board exercise its discretion to deny institution with respect to Ground 1 because Riedl was expressly considered by the Examiner during the prosecution of the '553 Patent. Prelim. Resp. 7–8. As noted in section I(E), above, in allowing claims 1–16 of the '533 Patent, the Examiner expressly referred to Riedl as the closest prior art, yet found that it "fails to teach . . . the instant claimed compounds." Ex. 2006, 913; *see also* Ex. 2005, 397, 569; Ex. 2006, 855 (same, with respect to similar claims).

Petitioner fails to mention that Riedl was cited during prosecution, let alone that the Examiner repeatedly highlighted Riedl as the closest prior art in the Examiner's Reasons for Allowance. Despite this omission, Petitioner implicitly asks us to second-guess the Examiner by instituting trial on the basis that Riedl anticipates claims 1–16. This we decline to do.

Pursuant to 35 U.S.C. § 325(d), we decline to institute trial with respect to Ground 1 because the Examiner repeatedly considered Riedl during prosecution, determined that Riedl was the closet prior art to the invention claimed, and expressly allowed the challenged claims over the Riedl reference. In the alternative, we further decline to institute trial with respect to Ground 1 on the merits, as discussed below.

iii. Analysis of Ground 1 on the Merits

"It is well established that the disclosure of a genus in the prior art is not necessarily a disclosure of every species that is a member of that genus." *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 999 (Fed. Cir. 2006). Rather, "whether a generic disclosure necessarily anticipates everything within the genus . . . depends on the factual aspects of the specific disclosure and the particular products at issue." *Sanofi–Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1083 (Fed. Cir. 2008). Of "critical importance" in conducting this analysis is "how one of ordinary skill in the art would understand the relative size of a genus or species in a particular technology." *OSRAM Sylvania, Inc. v. Am. Induction Techs., Inc.*, 701 F.3d 698, 706 (Fed. Cir. 2012). On the one hand, "when the class of compounds that falls within the genus is so limited that a person of ordinary skill in the art can '*at once envisage* each member of this limited class,' . . . a reference describing the genus anticipates every species within the genus." *In re Gleave*, 560 F.3d 1331, 1338 (Fed. Cir. 2009) (quoting *Eli Lilly & Co. v. Zenith Goldline Pharm., Inc.*, 471 F.3d 1369, 1376 (Fed. Cir. 2006)) (emphasis added). Conversely, where "the number of compounds actually disclosed by [the asserted prior art] numbers in the millions (including all proposed alternative substituents)," the prior art genus cannot anticipate a later species claim. *Eli Lilly*, 471 F.3d at 1376.

In addition to the raw number of disclosed compounds, a person of ordinary skill in the art would understand to look at any expressed "pattern of preferences" in the prior art, such as preferred embodiments, in assessing the scope of the generic disclosure. *Sanofi-Synthelabo v. Apotex, Inc.*, 470 F.3d 1368, 1377 (Fed. Cir. 2006). Therefore, to anticipate a later-claimed species, a pattern of preferences or other related teaching or suggestion must

lead to a genus small enough that a person of ordinary skill in the art would at once envisage the claimed species, e.g., "'a small recognizable class with common properties.'" *Sanofi-Synthelabo,* 550 F.3d at 1083 (citing *In re Ruschig*, 343 F.2d 965, 974 (CCPA 1965)).

In the present case, Petitioner argues Riedl discloses just such a sufficiently small genus, comprising "sorafenib . . . [and] three different examples of sorafenib with a single substitution on the middle benzene ring," specifically, methyl at position 3, chlorine at position 2/2', and chlorine at position 3/3'. Pet. 13–14, 16. Focusing on the two chlorinated compounds, Petitioner further reasons that,

> Riedl discloses both possible distinct positions for a single halogen substitution on the middle ring of sorafenib. There are only four suitable halogen groups specifically disclosed by Riedl: F, Cl, Br, or I. *Thus, there are eight individual chemical compounds possible when substituting a halogen (of one of the suitable halogen groups disclosed by Riedl) at one of these positions.* These eight possible compounds are disclosed and would be readily apparent to one of skill in the art who was looking to modify sorafenib. Therefore, Riedl expressly discloses the regorafenib compound, rendering claim 13 anticipated.

Id. at 16 (citing Ex. 1008 ¶¶ 49–54) (emphasis added).[8]

Patent Owner responds that Riedl does not expressly disclose regorafenib, the compound depicted in claim 13, but instead discloses a broad genus (Formula I) encompassing that compound. Prelim. Resp. 9. While the present record does not provide a precise estimate of the scope of this genus, Patent Owner suggests, not implausibly, that "Formula I

[8] Petitioner provides similar arguments with respect to claims 1–12, 14, and 16. *Id*. at 17–19.

encompasses well in excess of a billion compounds." Pet. 11–12. Irrespective of the actual number, we agree with Patent Owner that Formula I encompasses a vast number of species.

Where a reference does not "clearly and unequivocally disclose the claimed compound," to be anticipatory reference under 35 U.S.C. § 102, it must, nevertheless, "direct those skilled in the art to the compound without *any* need for picking, choosing, and combining various disclosures not directly related to each other by the teachings of the cited reference." *In re Arkley*, 455 F.2d 586, 587 (CCPA 1972). For the reasons set forth at pages 9–16 of the Preliminarily Response, we agree with Patent Owner that the genus relied on by Petitioner, having "'eight individual chemical compounds possible when substituting a halogen"—F, Cl, Br, or I—at position 2/2' or 3/3' of the central ring of sorafenib, does not exist in Riedl, and only results from Petitioner's improper picking and choosing disparate aspects of the disclosure. *See* Prelim. Resp. 13–15 (quoting Pet. 16).

Most particularly, Petitioner has not sufficiently established that Riedl discloses a genus comprising either (1) sorafenib with single substitutions on the middle benzene ring comprising chlorine at positions 2/2' and 3/3' (and, optionally, methyl at position 3), or (2) a derivative genus comprising eight singly-halogenated compounds corresponding to sorafenib substituted with F, Cl, Br, or I at position 2/2' or 3/3' of the central ring.[9] Accordingly, Petitioner fails to demonstrate why one of ordinary skill in the art would

[9] Petitioner does not argue that Riedl's 103 "Exemplified Compounds," discussed at pages 53–75 and depicted in the Tables at pages 76–88 of the reference, define a genus. *See* Prelim. Resp. 13.

read Riedl as disclosing a genus sufficiently small as to anticipate the species set forth in claim 13. *See Gleave*, 560 F.3d at 1337–38.

We also agree with Patent Owner that Petitioner's reasoning is legally insufficient to establish anticipation insofar as it requires that the genus of "eight possible compounds . . . would be readily apparent to one of skill in the art *who was looking to modify sorafenib*." *See* Prelim. Resp. 17–19 (referencing Pet. 16) (emphasis added). As aptly pointed out by Patent Owner, any desire to modify sorafenib relates to obviousness, not anticipation. *Id*. at 17–18; *see Callaway Golf Co. v. Acushnet Co.*, 576 F.3d 1331, 1347 (Fed. Cir. 2009) (noting that "motivation to combine is not an issue" in an "anticipation argument").

For the above reasons, Petitioner has not established a reasonable likelihood that claims 1–16 are anticipated by Riedl.

D. Ground 2: Obviousness in view of Riedl (Ex. 1002)

Petitioner asserts that claims 1–16 are rendered obvious in view of Riedl. Pet. 22–59. Patent Owner disagrees. Prelim. Resp. 21–36.

i. Analysis of Ground 2 Under 35 U.S.C. § 325(d)

Patent Owner requests that the Board exercise its discretion to deny institution with respect to Ground 2 because Riedl was expressly considered by the Examiner during the prosecution of the '533 Patent. Prelim. Resp. 36. As noted in section I(E), above, in allowing claims 1–16 of the '533 Patent, the Examiner expressly stated that although Riedl was the closest prior art, it "fails to . . . render obvious the instant claimed compounds . . . and does not fairly suggest their salts or pharmaceutical compositions." Ex. 2006, 913; *see also* Ex. 2005, 397, 569; Ex. 2006, 855 (same, with respect to similar claims).

Petitioner fails to mention that Riedl was cited during prosecution, let alone that the Examiner repeatedly highlighted Riedl as the closest prior art in the Examiner's Reasons for Allowance. Despite this omission, Petitioner implicitly asks us to second-guess the Examiner by instituting trial on the basis that Riedl anticipates claims 1–16. As with Ground I, pursuant to 35 U.S.C. § 325(d), we decline to institute trial with respect to Ground 2. In the alternative, we further decline to institute trial with respect to Ground 2 on the merits, as discussed below.

ii. Analysis of Ground 2 on the Merits

A claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The underlying analysis must include "articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006).

As in the case before us, the determination of whether a claimed compound would have been obvious over particular prior art compounds typically follows a two prong inquiry. *Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1291–93 (Fed. Cir. 2012). First, we determine "whether a chemist of ordinary skill would have selected the asserted prior art compounds as lead compounds, or starting points, for further development efforts." *Id.* at 1291. Second, we analyze whether there was a reason to modify a lead compound to make the claimed compound with a reasonable expectation of success. *Id.* at 1292; *see Eisai Co. v. Dr. Reddy's Labs., Ltd.*,

533 F.3d 1353, 1359 (Fed. Cir. 2008) (stating that even "post-*KSR*, a prima facie case of obviousness for a chemical compound still, in general, begins with the reasoned identification of a lead compound").

Petitioner argues that claim 13 is obvious over Riedl because

> Riedl discloses the structure of sorafenib . . . [and] "single halogen substitution [with chlorine] at position 3/3' and 2/2'. . . . Thus, there are two possible distinct positions at which a halogen can be substituted on the middle ring of sorafenib. As such, Riedl discloses both possible distinct positions for a single halogen substitution on the middle ring of sorafenib. There are only four suitable halogen groups specifically disclosed by Riedl: F, Cl, Br, or I. Thus, there are eight individual chemical compounds possible when substituting a halogen (of one of the suitable halogen groups disclosed by Riedl) at one of these positions. These eight possible compounds would be readily apparent to one of skill in the art who was looking to modify sorafenib. Therefore, Riedl expressly discloses the regorafenib compound, rendering claim 13 obvious over Riedl.

Id. at 21–22 (citing Ex. 1008 ¶¶ 61–63).[10]

As an initial matter, the above argument fails because, as discussed in section I(C)(iii), above, Riedl *does not* "expressly disclose[] the rografenib compound," as Petitioner contends. We further agree with Patent Owner's observation "that the Petition nowhere engages in a 'lead compound' analysis" and, at least with respect to Ground 2, "merely assumes—without explanation—that the POSA would select sorafenib for modification." Prelim. Resp. 22–23.

A lead compound comprises "a natural choice for further development efforts" (*Altana Pharma AG v. Teva Pharm. USA, Inc.*, 566 F.3d 999, 1008

[10] Petitioner provides similar arguments with respect to claims 1–12, 14, and 16. *Id*. at 22–25.

(Fed. Cir. 2009)), i.e., a prior art compound "that would be most promising to modify in order to improve upon its . . . activity and obtain a compound with better activity" (*Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357 (Fed. Cir. 2007)). "In determining whether a chemist would have selected a prior art compound as a lead, the analysis is guided by evidence of the compound's pertinent properties." *Otsuka Pharm.*, 678 F.3d at 1292. "Absent a reason or motivation based on such prior art evidence, mere structural similarity between a prior art compound and the claimed compound does not inform the lead compound selection." *Id*.

In setting forth Ground 2, Petitioner invokes a person of ordinary skill in the art "who was looking to modify sorafenib." Prelim. Resp. 22. Neither Petitioner nor Petitioner's expert address why a skilled artisan reading Riedl would select that compound for further development. Given that Riedl does not highlight any of the vast number of disclosed compounds as having particularly beneficial properties or present any enzymatic or biological data, we also do not discern from this reference why a person of ordinary skill in the art would have selected sorafenib as "a natural choice for further development efforts."

In addition, as discussed in the context of Grounds 3 and 4 below, Petitioner has not sufficiently established that a person of ordinary skill would have had a reason to modify a sorafenib to make the claimed compound with a reasonable expectation of success.

For each of the above reasons, Petitioner has not established a reasonable likelihood that claims 1–16 are rendered obvious by Riedl.

E. Grounds 3 and 4: Obviousness in view of Riedl (Ex. 1002) and Park (Ex.1004), and Further in View of Aherne (Ex. 1005)

Petitioner asserts that claims 1–16 are rendered obvious by the combination of Riedl and Park (Ground 4) and further in view of Aherne (Ground 3). Pet. 37–52, 25–37, respectively. Patent Owner disagrees. Prelim. Resp. 22–36. Because Petitioner's arguments substantially overlap, we consider them together, focusing in particular on Ground 3.

i. Overview of Park

Park discloses the potential benefits of adding one or more fluorine atoms to "alter the chemical properties, disposition, and biological activity of drugs." Ex. 1004, 443; *see, e.g., id*. at 445–446, 456 (exemplars with multiple fluorine atoms). In particular, Park teaches that "inclusion of a fluorine atom in a drug molecule can influence both the disposition of the drug and the interaction of the drug with its pharmacological target," with potential benefits on lipophilicity, pKa, tissue distribution, metabolism, pharmacodynamics, and toxicity. *Id*. at 443 (referencing Fig. 1).

In summarizing the potential benefits of fluorination, Park states:

> A large number of therapeutic agents contain strategically placed fluorine atoms. The introduction of fluorine into a molecule can alter both the rate and route of drug metabolism in a manner dependent on the site of fluorination in relation to the sites of metabolic attack. Fluorine substitution can also influence the tissue distribution of a drug, and fluorinated drugs have the distinct advantage that their in vivo tissue pharmacokinetics can be monitored noninvasively by 19F-labeled magnetic resonance spectroscopy. Substitution of fluorine for hydrogen at the site of oxidative attack can block metabolism, or deflect metabolism along an alternative route of metabolism. However, oxidative defluorination can occur in both aromatic and aliphatic systems, and therefore formal metabolic studies are always required when

> using fluorine substitution to determine the role of a particular biotransformation in a physiological or toxicological process.
>
> In terms of drug design, fluorine substitution can be used to alter the rate of drug metabolism and thereby produce a drug with a longer duration of action. Such an approach has already been used successfully for several classes of drugs. In addition, fluorine substitution can be used to reduce toxicity by blocking the formation of toxic metabolites and, in particular, chemically reactive metabolites. This can be achieved by fluorine substitution, at the appropriate site of the molecule, with an alteration in the balance between direct detoxication and metabolic bioactivation, provided the chemical modification does not impair drug efficacy.

Id. at 464.

ii. Overview of Aherne

Aherne states that "[h]igh-throughput screening is an essential component of the toolbox of modern technologies that improve speed and efficiency in contemporary cancer drug development" and presents "[e]xamples of successful drug discovery programmes based on high-throughput screening . . . [which] offer potential in the treatment of breast cancer and other malignancies." Ex. 1005, Abstract. Among these examples, Aherne discloses that sorafenib (BAY 43-9006) was "selected as a clinical candidate from a compound series identified in a biochemical screen of RAf-1 kinase activity." *Id*. at 152.

Aherne further teaches that the Lipinski Rule of 5 is a set of empirical rules that "can be used to predict whether a compound would be expected to have drug-like properties" and suggests that "hits from [high-throughput screening] may be assessed [according to these rules] before committing significant resource for chemical optimisation." *Id*. at 151. Although noting that not all successful drugs conform to these rules, Aherne states that "[t]he

basis for the Lipinski Rule of 5 is that most successful drugs have the following features: molecular weight, < 500 Da; log *P* [a measure of lipophilicity], <5; number of hydrogen bond donors, < 5; number of oxygen plus nitrogen atoms, <10." *Id*. Aherne Table 2 indicates that sorafenib comports with the Lipinksi Rule of 5. *Id*.

iii. Analysis

Petitioner relies on Aherne as disclosing sorafenib (BAY 43–9006) "for the treatment of RAF mediated diseases, including cancer" (Pet. 30 (citing Ex. 1005, 152)) and for the general principle "that it is desirable to optimize drug candidates" (*id*. at 25 (citing Ex. 1005, 149–151)). Petitioner further relies on Aherne as disclosing that sorafenib conforms to the Lipinski Rule of 5 as it has, for example, a molecular mass of less than 500 Daltons (482.82 D) and lipophilicity (measured as log *P*) of less than 5 (log *P* = 3.76). Pet. 30–31 (citing Ex. 1005, 151–152). Petitioner contends that Aherne teaches high-throughput screening "to quickly determine the best drug candidates," which may then be assessed using the Lipinski Rule of 5. *Id*. at 30 (citing Ex. 1005, 151).

Petitioner relies on Park as teaching that "[a]dding a fluorine was known to improve the pharmacological properties of a drug, such as improving the safety and efficacy of a drug, increasing stability, enhancing lipophilicity and increasing bioaccessibility, and producing a drug with a longer duration of action." *Id*. (citing Ex. 1004, 443–45, 447, 464). For reasons similar to those discussed above in section II(D)(ii), Petitioner argues that Riedl discloses 8 possible positions on sorafenib for single halogen substitutions. *See* Pet. 28. Moreover, Petitioner argues, only "two

distinct fluorinated compounds [] are formed with single fluorine substitution at one of these positions on that sorafenib middle ring." *Id*.

According to Petitioner, "it would have been obvious to a person of ordinary skill in the art to add a fluorine to sorafenib to make the claimed compound to obtain the [] benefits of fluorine substitution" taught by Park because "Riedl specifically taught adding a halogen in two possible distinct positions on the middle ring of sorafenib . . . and that halogen can be fluorine. Because there would be only a few possible molecules to test from these substitutions, selecting one that improved pharmacological properties, such as increased stability, lipophilicity, or bioaccessibilty, would be a matter of routine experimentation." *Id*. at 30, 33–34 (citations omitted).

Patent Owner argues that Grounds 3 and 4 fail because Petitioner makes no effort to engage in a "mandatory" lead compound analysis. Prelim. Resp. 22–25. While the Petition does lack a formal explanation of why one of ordinary skill in the art would have selected sorafenib as a lead compound, we find sufficient Aherne's disclosure that sorafenib was one of two drugs in the raf kinase signaling pathway "selected as a clinical candidate." *See* Ex. 1005, 152; *see also id.* (disclosing that identification of "the MEK inhibitor PD-098059 [] eventually led to the synthesis of the drug known as PD184352 . . . . [which] showed impressive preclinical activity and is currently in clinical trials."). *See Altana*, 566 F.3d at 1008 (indicating that the prior art may point to more than a "single lead compound for further development"); *see also Daiichi Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (no error in identifying five potential lead compounds).

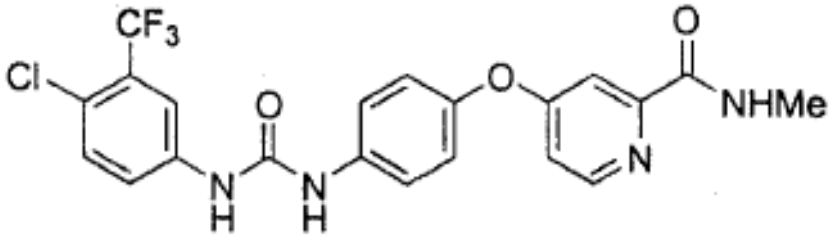
We do, however, agree with Patent Owner that "the Petition fails to provide a legally sufficient explanation as to why the POSA would have had a reason to substitute a fluorine atom at position three on [sorafenib's] central phenyl ring, and make no other changes, so as to produce regorafenib," for the reasons set forth in section II(A)(2) of the Preliminary Response, which we adopt. *See* Prelim. Resp. 25–33. That Riedl discloses a molecule equivalent to single substitutions of chlorine at the 2 or 3 position of sorafenib's central ring merely indicates that these positions can be halogenated. Petitioner has not adequately identified any pharmacological reason to do so, let alone to substitute chlorine for fluorine at that position. Thus, accepting that sorafenib is a lead compound, it nevertheless "remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner." *Takeda*, 492 F.3d at 1357.

Although Park discusses the potential benefits of fluorination, we do not read this reference to suggest that *any* fluorine substitution will result in improved pharmacological properties. As Patent Owner points out, were this true "all pharmaceutical compounds would be fluorinated, which is plainly not the case." Prelim. Resp. 28. To the contrary, Park emphasizes the "large number of therapeutic agents [that] contain *strategically placed* fluorine atoms," and expressly notes that certain targeted fluorinations are only desirable "provided the chemical modification does not impair drug efficacy." Ex. 1004, 465 (emphasis added).

Nor does Petitioner explain sufficiently why fluorination of the 3 position of the central ring of sorafenib would positively affect any particular property, such as efficacy, metabolism, or lipophilicity. *See* Prelim. Resp. 28–30. With respect to lipophilicity, for example, Aherne

discloses that sorafenib has a log *P* of 3.76—well within the limit suggested by Lipinski's Rule of 5 (log *P* < 3.76). *See* Ex. 1005, 151–152. Although Petitioner repeatedly suggests that the introduction of a fluorine atom increases lipophilicity, it provides no evidence that one of ordinary skill in the art would have reason to increase the lipophilicity of sorafenib. Likewise, with respect to efficacy and metabolism, Petitioner presents no structure-function analysis suggesting that the addition of a fluorine atom at any *particular* location in the sorafenib structure—let alone at the 3 position of the central ring—would be expected to provide a positive effect. *See* Prelim. Resp. 28–30.

Even were we to accept Petitioner's general assertion that "[t]he introduction of fluorine into drugs was [] well known in the art for improved pharmacological properties, such as increased stability" Petitioner fails to acknowledge that sorafenib itself bears three fluorine atoms, as shown below:



The above structure depicts the structure of sorafenib, which includes a tri-fluorinated methyl group. *See* Pet. 27, 41, 49 (each citing Ex. 1006,[11] 74); *see also* Prelim. Resp. 27 (noting that Ex. 1006 discusses "'[t]he pharmacological superiority of fluorinated compounds *over their non-*

[11] Wakefield, *Fluorinated pharmaceuticals*, CHEMICAL TECHNOLOGY 74–78 (2000). Ex. 1006.

fluorinated analogues'"). Accordingly, Petitioner fails explain why one of ordinary skill in the art would have reason to add fluorine to an already (multi-) fluorinated molecule.

Conversely, were we to accept Petitioner's implicit presumption that more fluorine is better, Petitioner has not explained adequately why one of ordinary skill in the art would not add *multiple* additional fluorine atoms to sorafenib. The molecular weight difference between sorafenib (464.82 D) and the mono-fluorinated regorafenib (MW 482.82 D) is 18 D. *See* Pet. 30–31. Accordingly, the addition of a second fluorine would result in a molecule of MW 500.82, which exceeds Lipinski's MW limit of <500 D only by about 0.02 D or 0.16%. Given Aherne's teaching that not all successful drugs conform to Lipinski's rules, Petitioner has not established that one of ordinary skill in the art would focus solely on mono-fluorinated sorafenib.

For these reasons, and for the reasons set forth in section II(A)(2) of the Preliminary Response, Petitioner has not established a reasonable likelihood that claims 1–16 are rendered obvious by Riedl and Park (Ground 4) or Riedl and Park in view of Riedl (Ground 3).

F. Ground 5: Obviousness in view of Aherne and Park

Petitioner asserts that claims 1–16 are rendered obvious by the combination of Aherne and Park. Pet. 46–64. Patent Owner disagrees. Prelim. Resp. 22–36.

Petitioner's arguments with respect to Ground 5 are similar to those set forth with respect to Grounds 3 and 4, and fail to establish a reasonable likelihood that claims 1–16 are obvious for the reasons set forth above. Petitioner further argues that,

> Park teaches that although fluorine substitution of hydrogen "exerts only a minor steric demand at receptor sites," it could "alter the pKa, the dipole moments, and even the chemical reactivity and stability of neighboring functional groups." Ex. 1004 at p.444. Knowing this, a person of ordinary skill in the art would experiment with fluorine substitution of the parent compound sorafenib at the eight distinct carbon positions including position 3 for a compound that has favorable chemical reactivity and stability of neighboring functional groups as well as screened for enhanced pharmacological properties such as stability and efficacy. Ex. 1008 at ¶99. Fluorine substitution at position 3 instead of position 2 has the advantage of being further away from the functional group 2-(N-methylcarbamoyl)-4-pyridyloxy. Hence, fluorine substitution at position 3 of sorafenib to make the compound regorafenib is a position of key interest as taught by Park. Ex. 1008 at ¶99.

Pet. 50–51.

Again, Petitioner does not explain sufficiently why one of ordinary skill in the art would seek to fluorinate a tri-fluorinated molecule, let alone add a single fluorine atom at the 3 position of the central ring of sorafenib. Nor are we convinced that one of ordinary skill in the art would focus on the 3 as opposed to the 2 position of sorafenib central ring for fluorination in light of Park's express teaching that substitution of fluorine for hydrogen "exerts only a minor steric demand at receptor sites," as quoted above. Moreover, Petitioner has not identified a receptor site on sorafenib, let alone a reason to minimize the "minor" stearic effects of fluorine on the sorafenib's central ring. *See* Ex. 1004, 444 ("Despite the fact that fluorine has a greater size than hydrogen, several studies have demonstrated that it is a reasonable hydrogen mimic and exerts only a minor steric demand at receptor sites, at least for monofunctional analogues.").

As most clearly illustrated in Ground 5, Petitioner's obviousness arguments comprise improper invitations "to explore a new technology or

general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it." *In re O'Farrell*, 853 F.2d, 903 (Fed. Cir. 1988). On the present record, Petitioner has not explained sufficiently why one of ordinary skill in the art would have reason to substitute a single fluorine atom for hydrogen on sorafenib's central ring, so as to produce regorafenib, the compound set forth in claim 13. As in the present case, where a party "urges an obviousness finding by 'merely throw[ing] metaphorical darts at a board' in hopes of arriving at a successful result, but 'the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful,' courts should reject 'hindsight claims of obviousness.'" *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1070–71 (Fed. Cir. 2012) (citing *In re Kubin*, 561 F.3d 1351, 1359 (Fed. Cir. 2009)). Accordingly, applying the guidance of our reviewing court, we determine that Petitioner has not sufficiently demonstrated a reasonable likelihood that claims 1–16 are rendered obvious by the combination of Aherne and Park.

III. CONCLUSION

For the foregoing reasons, we determine that Petitioner has not shown there is a reasonable likelihood that it would prevail in proving the unpatentability of claims 1–16 of the '553 Patent.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that pursuant to 35 U.S.C. § 314(a), the Petition for *inter*

partes review of the ’553 Patent is denied.

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