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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

INITIATIVE FOR MEDICINES, ACCESS & KNOWLEDGE (I-MAK), INC.,
Petitioner,

v.

GILEAD PHARMASSET LLC,
Patent Owner.

IPR2018-00122
Patent 8,334,270 B2

Before LORA M. GREEN, GRACE KARAFFA OBERMANN, and WESLEY B. DERRICK, *Administrative Patent Judges*.

DERRICK, *Administrative Patent Judge*.

DECISION
Denying Institution of *Inter Partes* Review
35 U.S.C. § 314(a)

I. INTRODUCTION

Initiative for Medicines, Access & Knowledge (I-MAK), Inc. ("Petitioner") requests an *inter partes* review of claims 1, 2, 10–18, and 20–25 of U.S. Patent 8,334,270 B2 (Ex. 1001, "the '270 patent"). Paper 2 ("Pet."). Gilead Pharmasset LLC ("Patent Owner") filed a Preliminary Response. Paper 9 ("Prelim. Resp.").

We have authority to determine whether to institute an *inter partes* review. 35 U.S.C. § 314(b); 37 C.F.R. § 42.4(a). We may not institute an *inter partes* review "unless . . . 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(a). Applying that standard, for the reasons set forth below, we decline to institute an *inter partes* review because the Petitioner has not shown a reasonable likelihood that it would prevail in establishing the unpatentability of any challenged claim.

II. BACKGROUND

A. Related Proceedings

The parties identify a concurrently filed, second petition for *inter partes* review of the '270 patent, IPR2018-00121. Pet. 2; Paper 4, 3. Patent Owner also identifies additional petitions for *inter partes* review of additional patents: IPR2018-00119 and IPR2018-00120 for U.S. Patent No. 7,964,580 B2; IPR2018-00103 for U.S. Patent No. 7,429,572 B2; IPR2018-00125 for review of U.S. Patent No. 8,633,309 B2; and IPR2018-00126 for review of U.S. Patent No. 9,284,342 B2. Paper 4, 3.

B. The '270 Patent (Ex. 1001)

The '270 patent is directed to, *inter alia*, phosphoramidate prodrugs of a nucleoside derivative for treatment of viral infections in mammals, its ester, or a stereoisomer thereof. Ex. 1001, Abstract. The '270 patent also addresses methods of treatment, uses, and processes for preparing such compounds. *Id.* The '270 patent claims the benefit of priority of two earlier-filed provisional applications, 60/909,315, filed on March 30, 2007, and 60/982,309, filed on October 24, 2007. Ex. 1001, 1:4–9.

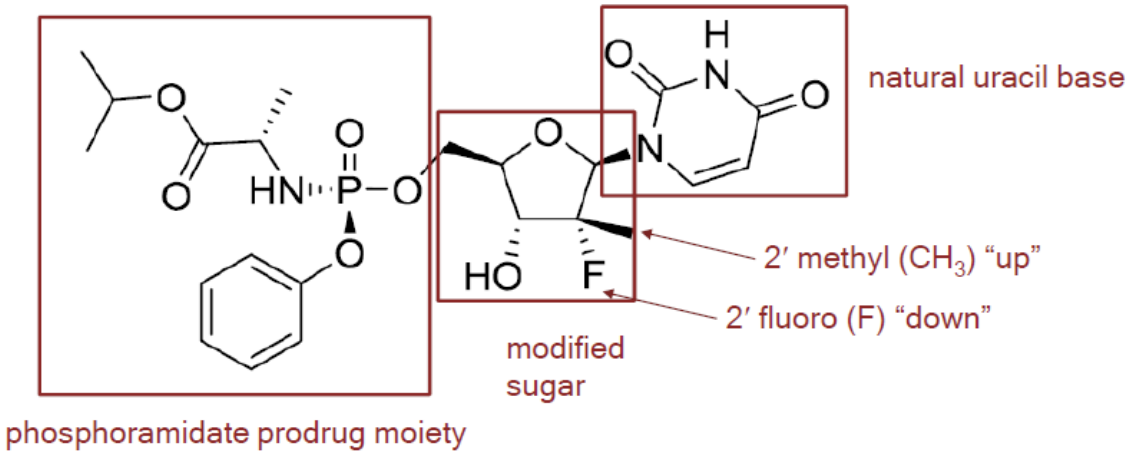
C. Illustrative Claims

Independent claims 1 and 16, each reciting a number of different phosphoramidate nucleoside derivatives, are reproduced below in part:

> 1. A compound selected from among
> . . .
> (S)-isopropyl 2-(((S)-(((2R,3R,4R, 5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyl[-]tetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate . . . .
>
> 16. A compound or its stereoisomer thereof selected from among
> . . .
> (S)-2-{[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahy-dro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid isopropyl ester . . . .

Ex. 1001, 605:35, 52–55, 607:58–59, 608:58–61.

The compound set forth by name in the reproduced portion of claim 1 above is the Sp stereoisomer of a phosphoramidate nucleoside derivative, known as sofosbuvir, which structure is depicted below:



Prelim. Resp. 3–4. The figure depicts the chemical structure of sofosbuvir with stereochemistry and identifies the compound's phosphoramidate prodrug moiety, modified sugar, and natural uracil base. *Id.* at 4. Claim 16 likewise, in setting forth a compound or stereoisomer of compounds identified by name, including that reproduced above, encompasses the Sp stereoisomer, the Rp stereoisomer, and mixtures of the two. *Id.* at 4, 11.

D. The Asserted Grounds of Unpatentability

Petitioner asserts that claims 1, 2, 10–18, and 20–25 of the '270 patent are unpatentable based on the following grounds. Pet. 3.

References	Statutory Basis
Clark '147,[1] Clark 2005,[2] and Perrone[3]	§ 103
Clark '147, Clark 2005, and McGuigan[4]	§ 103

[1] Clark, WO 2005/003147 A2, published January 13, 2005 (Ex. 1006).
[2] Clark et al., 48 J. MED. CHEM. 5504–08 (2005) (Ex. 1007).
[3] Perrone et al., 50 J. MED. CHEM. 1840–49 (2007) (Ex. 1008).
[4] McGuigan, WO 2005/012327 A2, published February 10, 2005 (Ex. 1009).

Petitioner supports the Petition with the testimony of Joseph M. Fortunak, Ph.D. (Ex. 1002). Based on Dr. Fortunak's statement of qualifications (*id.* ¶¶ 1–20) and curriculum vitae (Ex. 1003), on this record, we determine that he is qualified to opine from the perspective of a person of ordinary skill in the art.

III. ANALYSIS

A. Level of Ordinary Skill in the Art

Petitioner contends that a person of ordinary skill in the art would have held either

> (1) a Ph.D. in chemistry or a closely related field with some experience in an academic or industrial laboratory focusing on drug discovery or development, and would also have some familiarity with antiviral drugs and their design and mechanism of action, or
>
> (2) a Bachelor's or Master's degree in chemistry or a closely related field with significant experience in an academic or industrial laboratory focusing on drug discovery and/or development for the treatment of viral diseases.

Pet. 5–6 (citing Ex. 1002 ¶ 35).

Patent Owner does not expressly contest the level of ordinary skill. *See generally* Prelim. Resp.

On this record, we adopt Petitioner's essentially uncontested definition of the level of ordinary skill. We further note that the prior art itself demonstrates the level of skill in the art at the time of the invention. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (explaining that "specific findings on the level of skill in the art . . . [are not required] 'where the prior art itself reflects an appropriate level and a need for

testimony is not shown'" (quoting *Litton Indus. Prods., Inc. v. Solid State Sys. Corp.*, 755 F.2d 158, 163 (Fed. Cir. 1985))).

B. Claim Construction

In an *inter partes* review, the Board interprets claim terms in an unexpired patent according to their broadest reasonable construction in light of the specification of the patent in which they occur. 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2142 (2016) (affirming applicability of broadest reasonable construction standard to *inter partes* review proceedings). Under that standard, we interpret claim terms using "the broadest reasonable meaning of the words in their ordinary usage as they would be understood by one of ordinary skill in the art, taking into account whatever enlightenment by way of definitions or otherwise that may be afforded by the written description contained in the applicant's specification." *In re Morris*, 127 F.3d 1048, 1054 (Fed. Cir. 1997). "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." *Trivascular, Inc. v. Samuels*, 812 F.3d 1056, 1062 (Fed. Cir. 2016). If an inventor acts as his or her own lexicographer, the definition must be set forth with reasonable clarity, deliberateness, and precision. *Renishaw PLC v. Marposs Societa' per Azioni*, 158 F.3d 1243, 1249 (Fed. Cir. 1998). Only those terms which are in controversy need to be construed and only to the extent necessary to resolve the controversy. *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017).

Petitioner contends that "there is no reason to give any of the terms of the claims of the '270 [patent] a meaning other than their ordinary and accustomed meaning." Pet. 6.

Patent Owner does not contest that the claim terms should be given their ordinary and accustomed meaning. *See generally* Prelim. Resp. We determine that no claim term requires express construction for the purpose of determining whether to institute review.

C. Prior Art

1. Clark '147 (Ex. 1006)

Clark '147 teaches (2′R)-2′-deoxy-2′-fluoro-2′-C-methyl nucleosides, pharmaceutically acceptable salts, and prodrugs, and their use in treating hepatitis C infection. Ex. 1006, 1 (Abstract). Clark '147 teaches a general formula with substituents specified by reference to listings of what the substituents may be, some of which, if selected, would result in a phosphate or stabilized phosphate prodrug of (2′R)-2′-deoxy-2′-fluoro-2′-C-methyl uridine. Ex. 1006, 18:3–20:11, 47:16–25. Clark '147 also discloses that (2′R)-2′-deoxy-2′-fluoro-2′-C-methyl cytidine has anti-viral activity, including against HCV (*id.* at 88:16–89:30) and lower toxicity than certain other nucleoside analogs (*id.* at 90:1–27).

2. Clark 2005 (Ex. 1007)

Clark 2005 reports the synthesis of the (2′R)-2′-deoxy-2′-fluoro-2′-C-methyl analogs of both cytidine and uridine, these analogs' level of anti-HCV activity, and their level of cytotoxicity. Ex. 1007, 1, 3. Clark 2005 reports that the cytidine analog, i.e., compound 1, has anti-HCV activity and low cellular toxicity. *Id.* Clark 2005 reports that the uridine analog, i.e.,

compound 9, "demonstrated no activity or cytotoxicity in any assay." *Id.* at 3.

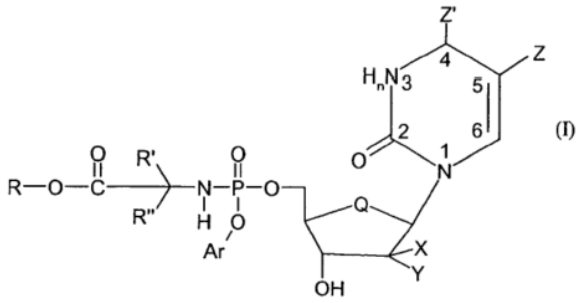
3. Perrone (Ex. 1008)

Perrone reports that "4′-[a]zidouridine did not inhibit HCV, although 4′-azidocytidine was a potent inhibitor of HCV replication under similar assay conditions" and that "4′-azidouridine triphosphate was a potent inhibitor of RNA synthesis by HCV polymerase." Ex. 1008, 1. Perrone reports the synthesis of a number of different phosphoramidate derivatives of 4′-azidouridine, their level of anti-HCV activity, and their level of cytotoxicity. *Id.* at 2–4. The derivatives include phenyl phosphoramidate and 1-naphthyl nucleotide derivatives,[5] including one derivative, compound 15, with a phenyl L-alanine isopropyl ester phosphoramidate moiety. *Id.* at 4. Perrone further teaches that the reported results "demonstrate[] the ability . . . to successfully bypass the rate limiting initial phosphorylation of a ribonucleoside analogue and thus confer significant antiviral activity on an inactive parent nucleoside." *Id.* at 5.

4. McGuigan (Ex. 1009)

McGuigan teaches nucleotide derivatives according to a general formula I, reproduced below, with substituents Ar, Q, R, R′, R″, X, Y, Z, and Z.

[5] Perrone states that "the phenyl substituent on the phosphate [of the phenyl phosphoramidate was replaced] with . . . 1-naphthyl" in the 1-naphthyl analogs. Ex. 1008, 4; *see also id.* (Scheme 3, Tables 1 & 3), *id.* at 4 (Fig. 2).



(I)

Ex. 1009, 5:11–14. Formula I depicts common structure and points of substitution with substituents. *Id.* McGuigan sets forth different possibilities for these substituents. *Id.* at 5:16–6:8, 7:22–13:22.

D. Alleged Unpatentability of the Challenged Claims

1. Obviousness over Clark '147, Clark 2005, and Perrone

Petitioner contends that claims 1, 2, 10–18, and 20–25 are unpatentable as obvious over the combination of Clark '147, Clark 2005, and Perrone. Pet. 28–44.

Claims 1 and 2 each "recite [a] Markush Group[] of compounds that include[s], '(S)-isopropyl 2-(((S)-(((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate,'" and claims 16–18 "recite [a] Markush [Group] of compounds that include, '(S)-2-{[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid isopropyl ester.'" *Id.* at 28 (citing Ex. 1001, 605:35–606:63, 607:57–616:23). The Petitioner identifies these compounds as "5'-phosphate (phosphoramidate) prodrugs of the uridine analog '(2'R)-2'-deoxy-2'-fluoro-2'-*C*-methyluridine', wherein the 5'-

phosphate group is the '*(phenyl)(isopropyl-L-alaninyl)phosphate*' group." *Id.* at 28–29 (citing Ex. 1001, 493:42–46; Ex. 1002 ¶ 160).

Petitioner sets forth its obviousness ground on the basis of one specific uridine analog—2'-deoxy-2'-fluoro-2'-C-methyluridine—with one specific phosphoramidate moiety—(phenyl)(isopropyl-L-alaninyl)phosphate. *See, e.g.*, Pet. 36 ("claims 1, 2, and 16-18 are different from Clark '147 only in that the stable 5'-phosphate group on the nucleoside analog . . . is the '(phenyl)(isopropyl-L-alaninyl)phosphate' group"); *id.* at 39 ("Applying Perrone's ProTide approach to Clark '147 and Clark 2005's promising nucleoside would result in *the compound* claimed in claims 1, 2, and 16-18 . . . . More specifically, Perrone taught that a stable modified 5'-phosphate group . . . is the '*(phenyl)(isopropyl-L-alaninyl)phosphate*' group . . . ." (emphasis added)); *id.* at 41–42 (relying on Perrone's teaching as to the "use of the '*(phenyl)(isopropyl-L-alaninyl)phosphate*' group"). In limiting its analysis in that way, Petitioner fails to set forth how, or if, any other compound recited in the Markush groups of claims 1, 2, and 16–18, would be rendered obvious by the cited references. *See generally* Pet.

Petitioner relies generally on Clark '147 and Clark 2005 for the 2′-deoxy-2′-fluoro-2′-C-methyluridine nucleoside and on Perrone for the phosphoramidate moiety. Petitioner contends that one of ordinary skill in the art, informed by the teachings of Clark '147 and Clark 2005, would have been led to 2′-deoxy-2′-fluoro-2′-C-methyluridine, a known nucleoside compound, and motivated "to use the well-known strategy to select a suitable stable 5'-phosphate group for (2'R)-2'-deoxy-2'-fluoro-2'-C-methyluridine . . . in order to increase its activity." *Id.* at 28–37. As to the "suitable stable 5'-phosphate group" (*id.* at 37), Petitioner contends that

"[o]ne would have been specifically motivated to refer to Perrone, which taught a phosphoramidate 'ProTide' approach to confer potency against hepatitis C virus by activating otherwise inactive nucleosides" (*id.* at 37–38).

Petitioner maintains Clark '147 suggests or teaches the nucleoside analog. Petitioner relies on Example 5 of Clark '147, which discloses that (2′R)-2′-deoxy-2′-fluoro-2′-C-methyl-*cytidine* has anti-viral activity, including against HCV (Ex. 1006, 88:16–89:30), and lower toxicity than certain other nucleoside analogs (*id.* at 90:1–27). Petitioner further relies on the common knowledge that uracil is one of the four bases in RNA, and contends that "a [person of ordinary skill in the art] would have been motivated to replace the cytidine in the active (2'R)-2'-deoxy-2'-fluoro-2'-C-methylcytidine 5'-triphosphate with a uridine," and also that they would have "had an expectation that this would produce a likewise active and potent HCV inhibitor." Pet. 33–34 (citing Ex. 1002 ¶ 168).

Petitioner maintains Clark '147 also suggests or teaches phosphorylated, or prodrug forms, of the nucleoside analog. Petitioner contends that "a [person of ordinary skill in the art] would have been . . . fully motivated to specifically choose, from the various compounds encompassed by Claim 40 [of Clark '147], the 5'-phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug) of (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl uridine as a practicable HCV inhibitor." Pet. 34 (citing Ex. 1002 ¶ 169). Petitioner further relies on a portion of Clark '147 that reads:

> A number of nucleotide prodrug ligands are known. <u>In general, alkylation, acylation or other liphophilic modification of the mono-, di- or triphosphate of the nucleoside reduces polarity and allows passage into cells</u>. . . . Any of these can be used in

> combination with the disclosed nucleosides to achieve a desired effect.

Pet. 35–36 (quoting Ex. 1006, 58:15–24, with added emphasis); Ex. 1002 ¶ 172. Petitioner contends Clark '147 "explicitly [teaches] that alkylation, acylation, arylation, or other lipophilic modification can be made to the phosphate group in the 5'-phosphate of (2'R)-2'-deoxy-2'-C-methyluridine to increase its activity, bioavailability and stability, and that the modified prodrug will convert into the 5'-monophosphate form (U'MP) after its entry into the cell." Pet. 36 (citing Ex. 1002 ¶ 173).

Clark 2005 discloses the nucleoside analog. Petitioner relies on Clark 2005's report that the (2′R)-2′-deoxy-2′-fluoro-2′-C-methyl analog of cytidine—compound 1—has anti-HCV activity and low cytotoxicity and that the uridine analog—compound 9—has "no activity or cytotoxicity in any assay." *Id.* at 36–37; Ex. 1007, 1, 3. Petitioner also relies on Clark 2005, without elaboration, as teaching "that the cytidine form of the Clark '147 nucleoside could metabolically convert *in vivo* to the uridine form." Pet. 36 (citing Ex. 1007, 3).

Petitioner contends that "[t]he Clark 2005 results would have motivated a [person of ordinary skill in the art] to understand the lack of activity of the uridine form and to pursue methods to activate the uridine if the lack of activity were due to inefficient phosphorylation." *Id.* at 37 (citing Ex. 1002 ¶ 178).

Petitioner also contends that "[a person of ordinary skill in the art] would investigate the 2'-deoxy-2'-fluoro-2'-C-methyluridine nucleoside in Clark 2005 as a lead compound." Pet. 41 (citing Ex. 1002 ¶ 189). In contending this, without explanation, Petitioner fails to specifically address its earlier contention, as to Clark '147, that "a [person of ordinary skill in the

art] would have been . . . fully motivated to specifically choose, from . . . the 5'-phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug) of (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl uridine as a practicable HCV inhibitor." Pet. 34 (citing Ex. 1002 ¶ 169). Rather, Petitioner simply settles, in effect, on the 2'-deoxy-2'-fluoro-2'-C-methyluridine nucleoside as its lead compound without adequate explanation, which suggests Petitioner relies on an improper hindsight reconstruction. Pet. 37, 41; *see* Prelim. Resp. 2 (persuasively arguing that Petitioner "provides no evidence to establish that the genus resulting from its proposed Clark '147/Clark 2005 combination is an appropriate starting point or that it is sufficiently narrow to define a lead compound").

As to the prodrug moiety, despite the teaching in Clark '147, identified above, that "[a] number of nucleotide prodrug ligands are known" and that "[a]ny of these can be used" (Pet. 35–36 (quoting Ex. 1006, 58:17, 23–24); Ex. 1002 ¶ 172), Petitioner contends that "[o]ne would have been specifically motivated to refer to Perrone [Ex. 1008], which taught a phosphoramidate 'ProTide' approach to confer potency against hepatitis C virus by activating otherwise inactive nucleosides" (Pet. 37–38). Petitioner's declarant identifies increased activity and reduced toxicity as improvements desired in modifying a lead compound. Ex. 1002 ¶ 32. Petitioner also contends, in respect to compositions, that "Perrone also taught that applying its phosphoramidate ProTide approach to nucleosides could activate them as HCV inhibitors for use in treating people." Pet. 43 (citing Ex. 1008, 1); Ex. 1002 ¶ 199.

Petitioner further contends that a person of ordinary skill in the art would have "had a reasonable expectation of success . . . because of the

general knowledge that nucleosides needed to be phosphorylated to [be] active in HCV replication and the fact that Perrone provided several examples of comparable nucleosides being triphosphorylated by its ProTide approach." Pet. 38–39; Ex. 1002 ¶ 182. Petitioner maintains that "[i]n considering the similarity of Clark '147, Clark 2005 and Perrone, a [person of ordinary skill in the art] would not focus on the structural differences between the parent nucleosides, 2′-deoxy-2′-fluoro-2′-C-methyluridine and 4′-aziduridne [sic, 4′-azidouridine]." Pet. 41; Ex. 1002 ¶ 189.

Petitioner refers to additional references, including Wagner (Ex. 1010), McGuigan 2006 (Ex. 1012), McGuigan 1994 (Ex. 1013), and Cahard (Ex. 1014), in discussing the background knowledge in the art (Pet. 15–21), and contends that "it was generally known that, for antiviral 5'-phosphate prodrugs, the antiviral activity lies in the nucleoside itself" (*id.* at 17 (citing Ex. 1002 ¶ 63)). Cahard is cited, in particular, for teaching "that the phenyl alanyl phosphoramidate approach was successful on a range of nucleosides by many research groups." *Id.* at 15–16 (citing Ex. 1002 ¶ 56; Ex. 1014, 1, 4).

Petitioner also contends that "the range of realistic options is reasonably limited" for substitutions to (or the identity of) the amino acid moiety, the ester on the amino group, the ester group on the phosphorus, and optional substitution on nitrogen of the amino acid. Pet. 18; Ex. 1002 ¶¶ 65–66. Petitioner cites to Perrone, without further analysis, as demonstrating "how the amino acid moiety is most often glycine, alanine or valine, and how the ester group on the amino acid is most often methyl, isopropyl, or benzyl," and contends, without cited support, that "[t]he useful ester groups

on phosphorous are aryl (typically phenyl)." Pet. 18; Ex. 1002 ¶¶ 65–66; Ex. 1008.

Although Petitioner cites to Wagner (Ex. 1010), McGuigan 2006 (Ex. 1012), McGuigan 1994 (Ex. 1013), and Cahard (Ex. 1014), including in referring to specific compounds, Petitioner provides little, if any, analysis as to the effects of the various disclosed substitutions (or identities) of various elements of the phosphoramidate moiety (*see, e.g.*, Pet. 17, 42 (citing Ex. 1012, 1, 4), 14–15, 17 (citing Ex. 1013, 3), 16–17 (citing Ex. 1014, 2–3)). Petitioner also does not provide particular analysis or evidence to support its implicit contention that the effect of any particular phosphoramidate, or other prodrug, moiety of a nucleoside analog prodrug is independent of the structure of the parent nucleoside analog. *See generally* Pet.

As to Perrone's disclosure, Petitioner emphasizes that "Perrone . . . prepared about 20 stable phosphate-based prodrugs of [4′-azidouridine]" (*id.* at 38), including compound 15 which has a phenyl L-alanine isopropyl ester phosphoramidate moiety (*id.* at 39). Petitioner maintains that "only 6 highly active phosphoramidate groups [are] particularly identified in Perrone (*i.e.* No.14, 15, 17, and 33–35)" and contends that "[a person of ordinary skill in the art] would have been motivated to try to attach each to the 5'-position of . . . (2'R)-2'-deoxy-2'-fluoro-2'-C-methyluridine resulting in the compounds of claims 1, 2, [and] 16–18." *Id.* at 40 (citing Ex. 1002 ¶ 186; Ex. 1008, 4). Petitioner further contends that a person of ordinary skill in the art "would in particular prepare the derivatives . . . that correspond to compounds 14, 15 and 17 in Perrone because they are described as having 'exceptional' antiviral activity." *Id.* at 41; Ex. 1002 ¶ 188; Ex. 1008, 3–4. As noted

above, however, the only analysis, or even mention of compounds recited in the claims, is limited to the two that Petitioner identifies as corresponding to the 5′-phosphate (phosphoramidate) prodrugs of (2R)-2-deoxy-2-fluoro-2-*C*-methyluridine, wherein the 5-phosphate group is the (phenyl)(isopropyl-L-alaninyl)phosphate group, the phosphoramidate moiety of Perrone's compound 15. *See generally* Pet.

Petitioner has, in effect, set forth two different, intertwined, theories of obviousness; a lead compound theory grounded on selection of 2′-deoxy-2′-fluoro-2′-C-methyluridine as a lead compound, followed by its modification, and a theory grounded on combining 2′-deoxy-2′-fluoro-2′-C-methyluridine, or the corresponding portion of a 5′-phosphate or stabilized prodrug, with the phosphoramidate moiety of a phosphoramidate 4′-azidouridine analog to arrive at claimed subject matter, in particular, the 5′-phosphate (phosphoramidate) prodrugs of (2R)-2-deoxy-2-fluoro-2-*C*-methyluridine, wherein the 5-phosphate group is the (phenyl)(isopropyl-L-alaninyl)phosphate group.

The lead compound analysis follows a two-part inquiry. In the first part, 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." *Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1291 (Fed. Cir. 2012). The question of whether a person of ordinary skill in the art would have selected a compound as a lead compound is "guided by evidence of the compound's pertinent properties." *Id.* at 1292. In the second part, we determine whether the artisan would have had reason to modify the lead compound to make the claimed compound, and whether they "would have had a reasonable expectation of success in doing so." *Id.*

As to the non-lead compound analysis, we simply determine whether "a skilled artisan would have had reason to combine the teaching of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success from doing so." *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1069 (Fed. Cir. 2012) (internal quotation marks and citation omitted). "Where a skilled artisan merely pursues 'known options' from 'a finite number of identified, predictable solutions,' the resulting invention is obvious under section 103." *Id.* at 1070 (quoting *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007)).

> Evidence of obviousness, especially when that evidence is proffered in support of an "obvious-to-try" theory, is insufficient unless it indicates that the possible options skilled artisans would have encountered were "finite," "small," or "easily traversed," and that skilled artisans would have had a reason to select the route that produced the claimed invention.

Id. at 1072 (citing *Ortho–McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008)).

Although Patent Owner presents its arguments generally as addressing deficiencies as to a lead compound theory of obviousness (Prelim. Resp. 12–16), some arguments are applicable to both theories (*id.* at 16–29).

Patent Owner argues that Petitioner has failed to establish the requisite motivation to combine the 2′-deoxy-2′-fluoro-2′-C-methyluridine nucleoside with any of Perrone's phosphoramidate moieties, and particularly (phenyl)(isopropyl-L-alaninyl)phosphate. Prelim. Resp. 26–29. Patent Owner further argues that Petitioner ignores structural differences between 2′-deoxy-2′-fluoro-2′-C-methyluridine and Perrone's 4′-azidocytidine nucleoside and that such differences "can have a huge impact on the

properties of the final molecule, including whether the molecule is effective against HCV and whether it has toxic side effects." *Id.* at 27–28. Patent Owner further argues that Petitioner "offers no evidence . . . that a person of ordinary skill would disregard these structural differences." *Id.* at 28 (citing Pet. 37–41; Ex. 1002 ¶¶ 182, 189).

Patent Owner contends that "for a different nucleoside compound one would need to conduct research to determine which phosphoramidate prodrugs may or may not work." *Id.* at 28–29. Patent Owner cites to Perrone itself as teaching that "the disclosed phosphoramidate prodrugs would be expected to behave differently if used with different parent compounds" in having "noted that 'quite distinct [structure-activity relationships]' were found for the particular nucleoside studied compared to nucleosides previously studied." Prelim. Resp. 28 (citing Ex. 1008, 4). Perrone also reports, in discussing certain phosphoramidate variants:

> These results [with 4′-azidouridine] were striking when compared to the 60–70 fold reduction in anti-HIV potency for d4T ProTides with an L-alanine to glycine replacement and a 20–40 fold reduction for the corresponding abacavir ProTides. This reinforces our earlier conclusion that *a separate ProTide motif optimization process is needed for each nucleoside analogue* versus a given target.

Ex. 1008, 4 (emphasis added) (endnotes omitted).

Patent Owner similarly contends that "[a] person of ordinary skill . . . would not have had a reasonable expectation that combining Perrone's phosphoramidate with 2'-deoxy-2'-fluoro-2'-C-methyluridine would yield an effective anti-HCV drug." Prelim. Resp. 29. Patent Owner, in discussing the search for "effective treatments for HCV" (*id.* at 4–10), highlights that both activity and toxicity are factors (*id.* at 6) and that "changes to the

structure of a nucleoside, or a prodrug used with a nucleoside, could have unpredictable and often negative impacts on the activity and toxicity of that nucleoside" (*id.*).

We have considered Petitioner's arguments and evidence along with the Preliminary Response, and, on this record, for reasons that follow, we agree with Patent Owner that Petitioner has not met the threshold for instituting an *inter partes* review of the '270 patent.

We turn first to the lead compound analysis. As set forth above, Petitioner contends that Clark '147 "explicitly taught that alkylation, acylation, arylation, or other lipophilic modification can be made to the phosphate group in the 5'-phosphate of (2'R)-2'-deoxy-2'-fluoro-2'-C-methyluridine" for improved properties and that "the 5'-phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug) . . . [are] practicable HCV inhibitor[s]" providing increased activity, bioavailability, and stability. Pet. 34, 36; Ex. 1002 ¶¶ 169, 173.

In selecting the 2'-deoxy-2'-fluoro-2'-C-methyluridine nucleoside as the lead compound, Petitioner fails to adequately explain why this particular compound was chosen over other compounds, particularly the monophosphate, or any of a number of stabilized monophosphate prodrugs. *See generally* Pet.

Also, as set forth above, Petitioner and its declarant contend that one of ordinary skill in the art—with the known nucleoside 2′-deoxy-2′-fluoro-2′-C-methyluridine in hand—would turn first to Perrone for its teaching of phosphoramidate prodrug moieties, and then to those moieties that provide greater activity, without significant toxicity, in phosphoramidate

4′-azidouridines. The difficulty, however, is that Petitioner fails to set forth a sufficient showing that a person of ordinary skill in the art would have had a reasonable expectation of the same benefit with 2′-deoxy-2′-fluoro-2′-C-methyluridine.

Petitioner relies variously on asserted similarity in structure of the parent nucleosides without directly addressing the structural differences (Pet. 41; Ex. 1002 ¶ 189) and on the notion that the antiviral activity lies on the nucleoside itself (Pet. 17). This reliance is insufficient, however, in light of potentially significant differential effects on activity (and toxicity) when a particular phosphoramidate moiety is used to modify different nucleoside analogs, as highlighted by Patent Owner. *See, e.g.*, Prelim. Resp. 28–29.

Petitioner's citation to other references that disclose phosphoramidate nucleoside analog prodrugs, likewise, as discussed above, is inadequate to support trial institution because there is insufficient analysis by Petitioner, particularly as to the likelihood of obtaining useful activity without significant toxicity. *See, e.g.*, Pet. 9–17, 19–21, and 42. That is to say, in the face of evidence that the effect of a particular phosphoramidate moiety of a nucleoside analog prodrug is not independent of the structure of the parent nucleoside analog, more is required of Petitioner than general assertions that the nucleoside analogs are similar, and that similar approaches with other nucleoside analogs provided success.

Under a non-lead compound analysis, Petitioner has likewise failed to set forth a sufficient basis for obviousness, within the meaning of 35 U.S.C. § 103, to meet its threshold burden. "[O]bviousness concerns whether a skilled artisan not only *could have made* but *would have been motivated to make* the combinations or modifications of prior art to arrive at the claimed

invention." *Belden Inc. v. Berk-Tek LLC*, 805 F.3d 1064, 1073 (Fed. Cir. 2015). The deficiency as to a reasonable expectation of success in obtaining an active and nontoxic agent, discussed above, is also relevant here because it goes to whether there are "identified, predictable solutions" that the skilled artisan would have been motivated to pursue at the time of the invention. *Cf. Cyclobenzaprine Hydrochloride*, 676 F.3d at 1070.

Further, Petitioner provides no sound basis for "the possible options skilled artisans would have encountered [being] 'finite,' 'small,' or 'easily traversed.'" *Id.* at 1072 (citing *Ortho–McNeil Pharm.*, 520 F.3d at 1364). Although Petitioner contends the skilled artisan would have selected from the subset of phosphoramidate moieties associated with high activity and low toxicity when used with 4′-azidouridine disclosed in Perrone (Pet. 40–41), there is no showing by Petitioner that these options would have been the only ones expected to provide high activity and low toxicity (*see generally id.*). Likewise, there is insufficient explanation and support for the range of possible phosphoramidate being finite, small, or easily traversed.

Dr. Fortunak's declaration essentially parrots the Petition without directing us to adequate objective proof for the bare assertions made therein, and, therefore, does not remedy the various deficiencies in Petitioner's ground of unpatentability. *See Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 294 (Fed. Cir. 1985) ("Lack of factual support for expert opinion going to factual determinations" is sufficient to "render the testimony of little probative value in a validity determination.").

Petitioner thus fails to bear the burden required to support institution of review. *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016) ("In an [*inter partes* review], the petitioner has the burden from the

onset to show with particularity why the patent it challenges is unpatentable."). Petitioner should not expect the Board to search the record to piece together what may support a challenge. *See* 37 C.F.R. § 42.22(a)(2) (a petition must include "[a] full statement of the reasons for the relief requested"); *DeSilva v. DiLeonardi*, 181 F.3d 865, 866–67 (7th Cir. 1999) ("A brief must make all arguments accessible to the judges, rather than ask them to play archaeologist with the record."); *cf. Magnum Oil Tools Int'l Ltd.*, 829 F.3d 1364, 1380–81 (Fed. Cir. 2016) (rejecting an argument that the Board properly "ma[de] an obviousness argument on behalf of [petitioner]" that "could have been included in a properly drafted petition," because "petitioner . . . bears the burden of proof").

Accordingly, we are not persuaded that Petitioner establishes a reasonable likelihood of prevailing in showing that the subject matter of any challenged claim is unpatentable over the combination of Clark '147, Clark 2005, and Perrone.

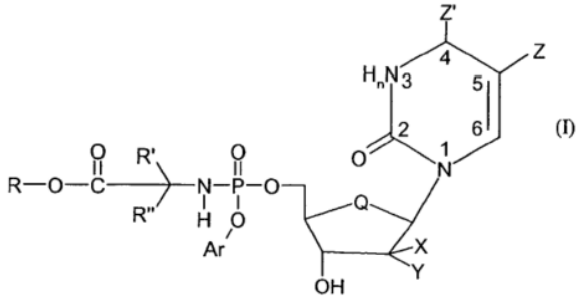
2. Obviousness over Clark '147, Clark 2005, and McGuigan

Petitioner contends that claims 1, 2, 10–18, and 20–25 are unpatentable as obvious over the combination of Clark '147, Clark 2005, and McGuigan. Pet. 45–58.

Petitioner contends, in the same manner as for the first ground, that one of ordinary skill in the art, informed by the teachings of Clark '147 and Clark 2005, would have been led to 2′-deoxy-2′-fluoro-2′-C-methyluridine and motivated "to use the well-known strategy to select a suitable stable 5'-phosphate group for (2'R)-2'-deoxy-2'-fluoro-2'-C-methyluridine . . . in order to increase its activity." *Compare* Pet. 45–54, *with id.* at 28–37.

The second ground also rests on the contention, as did the first, that the relied on prior art would have led the skilled artisan to "5'-phosphate (phosphoramidate) prodrugs of the uridine analog '(2'R)-2'-deoxy-2'-fluoro-2'-*C*-methyluridine', wherein the 5'-phosphate group is the '*(phenyl)(isopropyl-L-alaninyl)phosphate*' group." *Compare id.* at 45–46, *with id.* at 28–29; *see, e.g.*, *id.* at 53 ("claims 1, 2, and 16-18 are different from Clark '147 only in that the stable 5'-phosphate group on the nucleoside analog . . . is the '(phenyl)(isopropyl-L-alaninyl)phosphate' group"); *id.* at 55–57 (setting forth the necessary selections from McGuigan's disclosure to arrive at the (phenyl)(isopropyl-L-alaninyl)phosphate and concluding that "it would have been obvious . . . to obtain *the compound* of claims 1, 2 and 16–18" (emphasis added)).

Petitioner further contends that "[o]ne would have been specifically motivated to refer to" McGuigan's formula I—reproduced below—and then to select particular substituents from the listed, possible substituents. *Id.* at 55–57.



Ex. 1009, 5:11–14. Formula I depicts common structure and points of substitution with substituents. *Id.* McGuigan sets forth different possibilities for these substituents. *Id.* at 5:16–6:8, 7:22–13:22. Petitioner emphasizes, by underlining, the selection of methyl and F from "the group

comprising H, F, Cl, Br, I, OH, and methyl (-CH_3)" for X and Y and that "Z′ is =O" rather than -NH_2. Pet. 55–56; Ex. 1002 ¶ 223.

As to the necessary selections to arrive at the phosphoramidate moiety, referring to quoted sections of McGuigan as to what is preferred, Petitioner argues that "a [person of ordinary skill in the art] would have been encouraged by McGuigan . . . to select Q=O, n=1, Z'=O, Z=H, X=-CH_3, Y-F, Ar=phenyl, R=isopropyl, R'=H, and R"=-CH_3" such that "the compound of formula (I) of McGuigan . . . would be identical to the compound of claims 1, 2, 16–18."[6] *Id.* at 56 (citing Ex. 1002 ¶ 225). The Petition and relied on declaration both set forth that McGuigan "highlight[s] that, '[p]referably, R is methyl, ethyl, *n*- or *i*-propyl" (citing McGuigan 9:20) and, as to Ar, that "[m]ore preferably, Ar is selected from the group comprising: Ph-" (citing McGuigan 13:1–2). Pet. 56; Ex. 1002 ¶ 224.

Petitioner further contends that "[a person of ordinary skill in the art] would have been motivated to select these substituents because they were indicated by McGuigan . . . to be preferred and Clark '147 and Clark 2005 taught the same exact sugar ring and base structure." Pet. 56 (citing Ex. 1002 ¶ 225).

Petitioner contends that "[t]hus, it would have been obvious to a person skilled in the art to obtain the compound of claims 1, 2 and 16–18 based on Clark '147, Clark 2005 and McGuigan . . . in combination with the general knowledge in the art at the time." *Id.* at 56–57 (citing Ex. 1002 ¶ 226).

[6] In McGuigan's formula (I), these selections, with those above as to the nucleoside, would set forth the 5′-phosphate (phosphoramidate) prodrugs of the uridine analog 2′-deoxy-2′-fluoro-2′-C-methyluridine, wherein the 5′-phosphate group is the (phenyl)(isopropyl-L-alaninyl)phosphate group.

As Patent Owner points out, however, Petitioner omits substituents that McGuigan lists in the groups as similarly preferred, and ignores substituents identified as more preferred. *Compare* Prelim. Resp. 34–35, *with* Pet. 56. As to substituent R, the relied on group is not limited to "methyl, ethyl, *n*- or *i-propyl*" (Pet. 56 (emphasis omitted)), but also includes "*n*- or *i*-butyl (-C_4H_9) or benzyl (-$CH_2C_6H_5$)" (Ex. 1009, 9:20–21). Further, McGuigan states in "[t]he next sentence . . . that '[m]ost preferably, ***R is benzyl***.'" Prelim. Resp. 34 (quoting Ex. 1009, 9:21, with added emphasis). As to substituent Ar, similarly, the relied on group is not limited to a Ph-, but also includes "*p*$CF_3CH_6H_4$-, *p*$NO_2C_6H_4$-, *p*ClC_6H_4- and *o*ClC_6H_4-." Ex. 1009, 13:1–2; *see also* Prelim. Resp. 34–35. Petitioner and Dr. Fortunak thus err in setting forth what McGuigan identifies as preferred from which one of ordinary skill in the art would select substituents. On this record, Petitioner's selection of the requisite compounds suggests an impermissible hindsight reconstruction.

Also, as highlighted by Patent Owner's arguments contrasting the intended use of McGuigan's phosphoramidate derivatives (Prelim. Resp. 30–31), Petitioner fails to provide a rationale why a person of ordinary skill would look to McGuigan for its teachings, but only asserts that "[o]ne would have been specifically motivated to refer to [McGuigan's] teaching of compounds of formula (I)" (Pet. 55; Ex. 1002 ¶ 223). Petitioner directs us to no persuasive evidence nor explanation why McGuigan's formula (I), which is described as "particularly applicable for the treatment of a patient having breast cancer, colon cancer or prostate cancer" (Ex. 1009, 17:1–2), "would be useful to treat HCV, which is a disease of the liver" (Prelim. Resp. 31).

Petitioner's failure to identify evidence sufficient to support the contention that one of ordinary skill in the art would have been motivated to select the particular substituents required to arrive at the claimed subject matter, including even the particular compound relied on in Petitioner's contention of obviousness, and is dispositive. Here again, Dr. Fortunak's declaration essentially parrots the Petition without directing us to adequate objective proof for the bare assertions made therein, and, therefore, does not remedy this deficiency. *See Ashland Oil*, 776 F.2d at 294. Lacking any sound basis for why one of ordinary skill would select the particular substituents, this ground of obviousness lacks the requisite "rational underpinning [required] to support the legal conclusion of obviousness." *KSR*, 550 U.S. at 418 (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)). Petitioner thus fails to bear the burden required to support institution of review. *Harmonic*, 815 F.3d at 1363.

Accordingly, we are not persuaded that Petitioner establishes a reasonable likelihood of prevailing in showing that the subject matter of any challenged claim is unpatentable over Clark '147, Clark 2005, and McGuigan.

IV. CONCLUSION

Petitioner has not established a reasonable likelihood of prevailing on its assertion that claims 1, 2, 10–18, and 20–25 are unpatentable.

V. ORDER

For the reasons given, it is:

ORDERED that the Petition is *denied* as to all challenged claims of the ’270 patent and no trial is instituted.

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