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Paper No. 7
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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

Case IPR2018-00126
Patent 9,284,342 B2

Before LORA M. GREEN, ERICA A. FRANKLIN, and RICHARD J. SMITH, *Administrative Patent Judges.*

SMITH, *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") filed a Petition (Paper 2, "Pet.") to institute an *inter partes* review of claims 1–4 of U.S. Patent 9,284,342 B2 (the "'342 patent"). 35 U.S.C. § 311. Gilead Pharmasset LLC ("Patent Owner") filed a Preliminary Response to the Petition. Paper 6 ("Prelim. Resp.").

We have authority to determine whether to institute an *inter partes* review under 35 U.S.C. § 314. To institute an *inter partes* review, we must determine that the information presented in the Petition shows "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). For the reasons set forth below, we conclude that Petitioner has not established a reasonable likelihood that it would prevail in showing the unpatentability of any challenged claim of the '342 patent. Therefore, we do not institute an *inter partes* review for any challenged claim of the '342 patent.

A. Related Proceedings

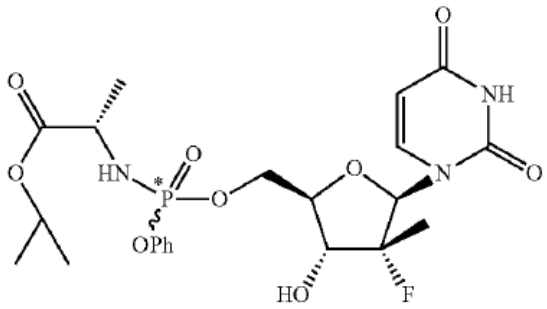
Petitioner also filed two petitions for *inter partes* review of U.S. Patent No. 7,964,580 (Case Nos. IPR2018-00119 and IPR2018-00120); two petitions for *inter partes* review of U.S. Patent No. 8,334,270 (Case Nos. IPR2018-00121 and IPR2018-00122); one petition for *inter partes* review of U.S. Patent No. 7,429,572 (Case No. IPR2018-00103); and one petition for *inter partes* review of U.S. Patent No. 8,633,309 (Case No. IPR2018-00125). Pet. 2; Paper 3, 3.

B. The '342 Patent

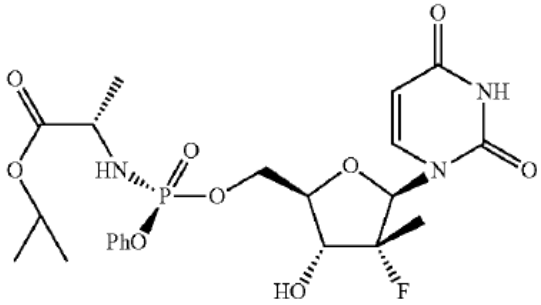
The '342 patent relates to nucleoside phosphoramidates and their use as agents for treating viral diseases, such as hepatitis C. Ex. 1001, Abstract; 1:21–26. The '342 patent discloses a compound represented by formula 4 and its respective

phosphorous-based diastereomers represented by formulas S*p*-4 and R*p*-4, as shown below:

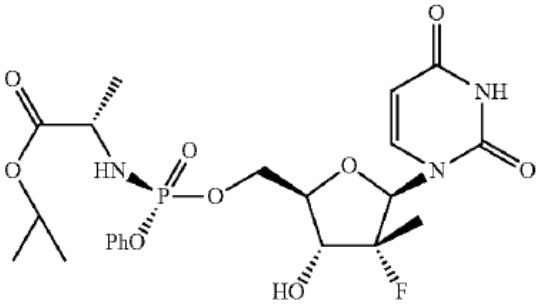
4



S_P-4



R_P-4



Id. at 4:65–5:34. The ’342 patent states that “[t]he term ‘P*’ means that the phosphorus atom is chiral and that it has a corresponding Cahn-Ingold-Prelog designation of ‘R’ or ‘S’ which have their accepted meanings.” *Id.* at 6:28–30. The compound of formula S*p*-4 is sofosbuvir. Prelim. Resp. 9.

The ’342 patent discloses six crystalline forms of S*p*-4 (Forms 1–6). Ex. 1001, 73:51–76:43. X-ray powder diffraction (XRPD) 2θ-reflections are attributed to Form 6, and recited in claim 1. *Id.* at 76:10–43. The ’342 patent

characterizes Form 6, such as by X-ray powder diffraction, and describes methods for preparing Form 6. *Id.* at 73:10–50; 82:1–11, 41–42.

The ’342 patent states that “U.S. patent application Ser. No. 12/053,015, which corresponds to WO 2008/121634 [Sofia ’634, Ex. 1005] . . . discloses a number of phosphoramidate nucleoside prodrugs, many of which show activity in an HCV assay.” *Id.* at 4:55–59. During prosecution, the Examiner expressly addressed Sofia ’634, stating in the Notice of Allowance that:

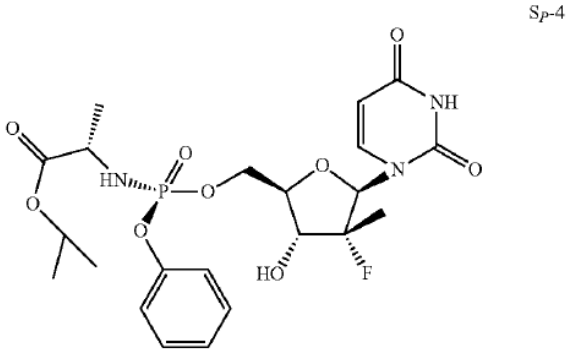
> The claimed invention is seen to be novel and non-obvious over the prior art. The prior art does not disclose a crystalline composition of the claimed compound having the claimed XRPD peaks. References to the claimed compound in the prior art (see for example [Sofia ’634]) [do] not disclose the specific crystal structure described in the claims, or a method of preparing a crystalline form of the compound that would have resulted in that particular crystal. Because of the unpredictability of crystalline polymorphs, one of ordinary skill in the art would not have been able to, based on the prior art disclosure, predict or make this particular crystal form.

Ex. 1004, 183–184.

C. Illustrative Claim

Petitioner challenges claims 1–4 of the ’342 patent, of which claim 1 is the only independent claim. Claim 1 is reproduced below:

1. A crystalline compound represented by the formula (S*p*-4):



having XRPD 2θ-reflections (°) at about: 6.1 and 12.7.

Ex. 1001, 89:42–65.

Claims 2–4 depend directly or indirectly on claim 1.[1] *Id.* at 90:1–9.

D. The Asserted Grounds of Unpatentability

Petitioner contends that the challenged claims are unpatentable under 35 U.S.C. §103(a) based on the following specific grounds. Pet. 3.

Reference[s]	**Basis**	**Claims challenged**
Sofia '634[2] and Sofia 2010[3]	§ 103(a)	1–4
Sofia '634 and Ma[4]	§ 103(a)	1–4
Clark '147[5] and Ma	§103(a)	1–4

Petitioner also relies on the Declaration of Joseph M. Fortunak, Ph.D. Ex. 1002.

[1] For example, claim 3 recites "[a] method of treating a hepatitis C virus infection in a human comprising administering to the human an effective amount of the crystalline compound according to claim 1." Ex. 1001, 90:4–6.
[2] Sofia et al., WO 2008/121634 A2, published Oct. 9, 2008 ("Sofia '634"). Ex. 1005.
[3] M.J. Sofia et al., *Discovery of a β-D-2'-Deoxy-2'-α-fluoro-2'-β-C-methyluridine Nucleotide Prodrug (PSI-7977) for the Treatment of Hepatitis C Virus*, J. MED. CHEM. 53, 7202–18 (2010) ("Sofia 2010"). Ex. 1014.
[4] H. Ma et al., *Characterization of the Metabolic Activation of Hepatitis C Virus Nucleoside Inhibitor β-D-2'-Deoxy-2'-fluoro-2'-C-methylcytidine (PSI-6130) and Identification of a Novel Active 5'-Triphosphate Species*, J. OF BIOLOGICAL CHEM., 282, 29812–20 (2007) ("Ma"). Ex. 1010.
[5] Clark, WO 2005/003147 A2, published Jan. 13, 2005 ("Clark '147"). Ex. 1007.

II. ANALYSIS

A. Person of Ordinary Skill in the Art

Petitioner asserts that a person of ordinary skill in the art would have 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. 7–8.

Patent Owner's definition of a person of ordinary skill in the art differs from Petitioner's definition. Prelim. Resp. 11. Patent Owner contends that a person of ordinary skill in the art ("POSA") "would have at least a bachelor's degree in chemistry, pharmaceutical sciences or a related discipline, along with experience working in pharmaceutical solid product development and/or solid-state chemistry. Additionally, a POSA would have knowledge and experience, and/or access to others with knowledge and experience, in developing antiviral drugs." *Id.*

On this record and at this stage of the proceeding, we do not discern an appreciable difference in the parties' respective definitions of a person of ordinary skill in the art. Accordingly, we find that a person of ordinary skill in the art would have 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, including solid-state chemistry, 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, including solid-state chemistry, for the treatment of viral diseases.

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

B. Claim Construction

In an *inter partes* review, the Board interprets claim terms in an unexpired patent according to the broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R. § 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, and absent any special definitions, we generally give claim terms their ordinary and customary meaning, as would be understood by one of ordinary skill in the art at the time of the invention. *See In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). Any special definitions for claim terms must be set forth with reasonable clarity, deliberateness, and precision. *See In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

Neither Petitioner nor Patent Owner raise any claim construction issues or proposed constructions, and both acknowledge that the claim terms should be given their ordinary and customary meaning. Pet. 8; Prelim. Resp. 12. Accordingly, we apply the ordinary and customary meaning to the claims at issue. *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co. Ltd.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) ("[W]e need only construe terms 'that are in controversy, and only to the extent necessary to resolve the controversy'" (quoting *Vivid Techs.*,

Inc. v. Am. Sci. & Eng'g, Inc., 200 F.3d 795, 803 (Fed. Cir. 1999))).

C. Principles of Law

Obviousness "requires a suggestion of all limitations in a claim." *CFMT, Inc. v. Yieldup Int'l Corp*., 349 F.3d 1333, 1342 (Fed. Cir. 2003) (citing *In re Royka*, 490 F.2d 981, 985 (CCPA 1974)). "In determining whether obviousness is established by combining the teachings of the prior art, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art." *In re GPAC Inc.*, 57 F.3d 1573, 1581 (Fed. Cir. 1995) (internal quotations omitted).

Obviousness also requires "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *KSR Int'l Co. v. Teleflex Inc*., 550 U.S. 398, 418 (2007). A conclusion of obviousness "cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *Id.* (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)).

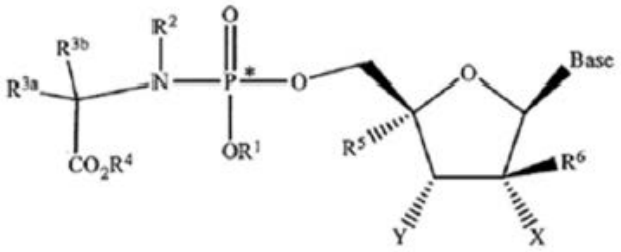
We analyze the asserted grounds of unpatentability in accordance with the above-stated principles.

D. Obviousness over Sofia '634 and Sofia 2010

Petitioner asserts that claims 1–4 are obvious over Sofia '634 and Sofia 2010. Pet. 32–39. On this record, we determine that Petitioner has not established a reasonable likelihood that it would prevail in showing that any of claims 1–4 are obvious over Sofia '634 and Sofia 2010.

1. Sofia '634 (Ex. 1005)

Sofia '634 discloses phosphoramidate prodrugs of nucleoside derivatives represented by formula (I):



I

Ex. 1005, Abstract. Sofia ’634 further describes nucleoside phosphoramidates and their use as agents for treating viral diseases, such as hepatitis C virus (HCV) infection. *Id.* at 2:15–21. Example 25 of Sofia ’634 is the same as that represented by formula (4) in the ’342 patent, except that Example 25 is a mixture of diastereomers at phosphorus. *Id.* at 684. Example 81 of Sofia ’634 describes the separation of diastereomeric mixtures of Examples 15, 39, and 49. *Id.* at 693–94. Sofia ’634 is referenced in the ’342 patent. Ex. 1001, 4:55–59.

2. Sofia 2010 (Ex. 1014)

Sofia 2010 relates to a nucleotide prodrug (PSI-7977) for the treatment of hepatitis C virus. Ex. 1014, Title. Sofia 2010 states that “[t]he single diastereomer **51** [PSI-7977] of diastereomeric mixture **14** was crystallized, and an X-ray structure was determined establishing the phosphoramidate stereochemistry as S*p*, thus correlating for the first time the stereochemistry of a phosphoramidate prodrug with biological activity.” *Id.*, Abstract. Sofia 2010 discloses the methylene chloride solvate of sofosbuvir (compound 51). *Id.*, Figure 5 at 8. Sofia 2010 was cited during the prosecution of the ’342 patent. Ex. 1001, 10.

3. Analysis

Petitioner contends that, based on the asserted teachings of Sofia ’634 and Sofia 2010, “a POSA would have been motivated to combine the teachings of Sofia ’634 and Sofia 2010 to pursue isolation and testing of the diastereomers of

the compounds taught in Sofia '634, as well as to search for alternative crystalline forms. EX1002 at ¶ 111. These crystalline forms would be structurally and functionally identical to the form claimed in claim 1 of the '342 patent. *Id.*" Pet. 36. The cited paragraph of the Fortunak Declaration repeats Petitioner's statement, without citation to any evidentiary support. *See* Ex. 1002 ¶ 111.

Petitioner further contends that "[t]he only difference between claim 1 of the '342 patent and the crystalline forms of Sophia '634 that a POSA would have isolated, tested and determined had superior properties – as taught by Sophia 2010 – is the recitation of certain XRPD 2Θ-reflections, such reflections having no utility in themselves. EX1002 at ¶112." Pet. 36. The cited paragraph of the Fortunak Declaration repeats Petitioner's statement, without citation to any evidentiary support. *See* Ex. 1002 ¶ 112. Nevertheless, according to Petitioner, "the XRPD 2Θ-reflections recited in claim 1 do not provide the stereoisomer any of its properties or any functionality," "are of no scientific or technical significance," and "are merely descriptive of some non-functional aspects of the XRPD 2Θ-reflections." Pet. 36. Again, Petitioner supports these statements by reference to the Fortunak Declaration, which merely repeats Petitioner's statements without citation to any evidentiary support. *See* Ex. 1002 ¶ 113.

Patent Owner states that "neither [Sofia '634 nor Sofia 2010] teaches or suggests Form 6 of sofosbuvir, or a crystalline form of sofosbuvir characterized by the recited XRPD reflections." Prelim. Resp. 17. In response to Petitioner's arguments regarding the claimed XRPD limitations, Patent Owner points to Petitioner's acknowledgement that the "difference in crystalline packing [is] a potential source of variability in properties, such as melting point, stability, aqueous solubility, formulation characteristics, bioavailability, bioequivalence, that are critical for understanding and controlling drug performance." *Id.* at 19, citing

Pet. 20. Patent Owner also characterizes Petitioner's motivation argument as "a general motivation to identify new crystalline forms," and therefore insufficient motivation to support an obviousness conclusion. *See* Prelim. Resp. 20–25.

On this record, Petitioner does not persuasively explain how Sofia '634 or Sofia 2010, alone or in combination, suggest the limitations of claim 1, or persuasively explain a reason that would have motivated a person of ordinary skill in the art to modify or combine the teachings of Sofia '634 and Sofia 2010 to arrive at the claimed invention. Claim 1 specifically recites crystalline compound S*p*-4 "having XRPD 2θ-reflections (°) at about: 6.1 and 12.7." Ex. 1001, 89:42–65. Those limitations define a crystal structure of the claimed compound. *See In re Grose*, 592 F.2d 1161, 1165 (CCPA 1979). But Petitioner does not persuasively establish that those limitations are suggested by Sofia '634 and/or Sofia 2010. *See CFMT*, 349 F.3d at 1342; *GPAC Inc.*, 57 F.3d at 1581.

Petitioner essentially disregards the crystalline structure limitations of claim 1 and argues that "[a]lthough a POSA would not have been able to predict this exact recitation of 2 XRPD 2Θ-reflections, a POSA would be able to prepare the S*p*-4 compound with such 2Θ-reflections." Pet. 36. But the argument that a POSA *could* have prepared the S*p*-4 compound having that structure is unpersuasive because "obviousness 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). Moreover, we find that Petitioner's arguments are generally conclusory in nature, without evidentiary support. *See KSR*, 550 U.S. at 418. Thus, Petitioner fails to persuasively establish that the claimed crystalline structure limitations are suggested by the prior art, or that a person of ordinary skill in the art would have been motivated to modify or combine Sofia '634 and/or Sofia

2010 to arrive at the invention of claim 1.

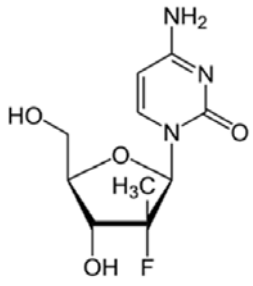
Accordingly, we determine that Petitioner has not shown a reasonable likelihood that it would prevail on its assertion that claim 1 (and dependent claims 2–4, which include the limitations of claim 1) are obvious over Sofia '634 and Sofia 2010. *See In re Fine*, 837 F.2d 1071, 1076 (Fed. Cir. 1988) ("Dependent claims are nonobvious under section 103 if the independent claims from which they depend are nonobvious.").

E. Obviousness over Sofia '634 and Ma

Petitioner asserts that claims 1–4 are obvious over Sofia '634 and Ma. Pet. 39–45. On this record, we determine that Petitioner has not established a reasonable likelihood that it would prevail in showing that any of claims 1–4 are obvious over Sofia '634 and Ma.

1. Ma (Ex. 1010)

Ma relates to the metabolism and mechanism of action of the compound PSI-6130, illustrated below:



PSI-6130

Ex. 1010; Pet. 31; Prelim. Resp. 15. Ma states that PSI-6130 "has been identified as a potent and selective inhibitor of HCV replication." Ex. 1010, 2. Ma was cited during the prosecution of the '342 patent. Ex. 1001, 10.

2. Analysis

Petitioner repeats essentially the same arguments as above regarding Sofia '634 and the crystalline structure limitations of claim 1, and our response to those arguments is as set forth above. *Compare* Pet. 36–38 *with* Pet. 42–44. Petitioner further argues that Ma teaches "the conversion of PSI-6130 into the uridine analog RO2433" and that the teachings in Ma "indicate that a monophosphate prodrug form of compound 1D/RO2433 was a very attractive drug candidate for the treatment of hepatitis C viral infections." Pet. 41–42. Petitioner supports its arguments by reference to page 1 of Ma (without pointing to any specific text) and a quote from page 8 of Ma regarding "longer intracellular half-life of RO2433-TP."[6] *Id.* Petitioner further advances the conclusory argument that

> [t]herefore, although Sofia '634 did not disclose the polymorph claimed in claim 1 of the '342 exactly (i.e., S_P-4), Ma highlighted RO2433 as a lead compound to pursue, and it would have been obvious for a POSA to take RO2433 and create stereoisomers as taught by Sofia '634 to arrive at multiple crystalline forms of its compounds.

Pet. 44. As support for that conclusory statement of obviousness, Petitioner again cites to the Fortunak Declaration that repeats the same statement without citing evidentiary support. Ex. 1002 ¶ 137.

Although Petitioner states that a POSA "would have been motivated to search for crystalline forms of RO2433" and "motivated to screen the limited number of crystalline forms possible" (Pet. 43–44), Petitioner does not persuasively establish that the crystalline structure limitations of claim 1 are suggested by Sofia '634 and/or Ma. *See CFMT*, 349 F.3d at 1342; *GPAC Inc.*, 57

[6] Petitioner also refers to the Fortunak Declaration which merely repeats the same statements advanced by Petitioner. See Ex. 1002 ¶¶ 127–130.

F.3d at 1581. Moreover, we again find that Petitioner's arguments are generally conclusory in nature, without evidentiary support. *See KSR*, 550 U.S. at 418.

Accordingly, we determine Petitioner has not established a reasonable likelihood that it would prevail in showing that claim 1 (and dependent claims 2–4 which include the limitations of claim 1) are obvious over Sofia '634 and Ma. *See Fine*, 837 F.2d at 1076.

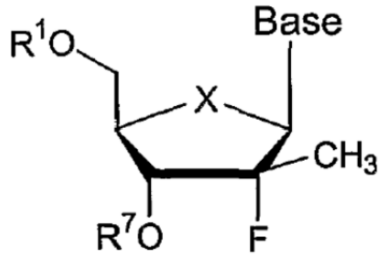
F. Obviousness over Clark '147 and Ma

Petitioner asserts that claims 1–4 are obvious over Clark '147 and Ma. Pet. 45–51. On this record, we determine that Petitioner has not established a reasonable likelihood that it would prevail in showing that any of claims 1–4 are obvious over Clark '147 and Ma.

1. Clark '147 (Ex. 1007)

Clark '147 is directed to compositions and methods for treating a *Flaviviridae* infection, such as hepatitis C virus, using (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleosides. Ex. 1007, Abstract. Clark '147 claims:

A (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside (β-D or β-L) or its pharmaceutically acceptable salt or prodrug thereof of the structure:



wherein Base is a purine or pyrimidine base; and substituents X, R^1, and R^7 are respectively one of a group of elements or compounds. *Id.* at 101. Clark '147 was cited during the prosecution of the '342 patent. Ex. 1001, 4.

2. Analysis

Petitioner argues that "[t]hese disclosures in Clark, combined with common knowledge in the art regarding polymorphs, polymorph screening, and crystallization of crystalline forms, would have motivated a POSA to pursue crystalline forms as drug candidates." Pet. 47. Petitioner supports this statement by reference to the same statement in the Fortunak Declaration that lacks any citation to evidentiary support. Ex. 1002 ¶ 147. Petitioner repeats the same arguments regarding Ma and the crystalline structure limitations of claim 1 as set forth above, and our response to those arguments is as set forth above. *Compare* Pet. 40–44 *with* Pet. 47–50. Similar to the argument set forth above, Petitioner concludes that

> [t]herefore, although Clark '147 did not disclose the polymorph claimed in claim 1 of the '342 exactly (i.e., S_P-4), Ma highlighted RO2433 as a lead compound to pursue, and it would have been obvious for a POSA to take RO2433 and create stereoisomers as taught by Clark '147 to arrive at multiple crystalline forms of its compounds.

Pet. 50. As support for that conclusory statement of obviousness, Petitioner again cites to the Fortunak Declaration that repeats the same statement without citing evidentiary support. Ex. 1002 ¶ 158.

Again, Petitioner does not persuasively establish that the crystalline structure limitations of claim 1 are suggested by Clark '147 and/or Ma. *See CFMT*, 349 F.3d at 1342; *GPAC Inc.*, 57 F.3d at 1581. Moreover, we again find that Petitioner's arguments are generally conclusory in nature, without evidentiary support. *See KSR*, 550 U.S. at 418.

Accordingly, we determine Petitioner has not established a reasonable likelihood that it would prevail in showing that claim 1 (and dependent claims 2–4

which include the limitations of claim 1) are obvious over Clark '147 and Ma. *See Fine*, 837 F.2d at 1076.

III. CONCLUSION

For the foregoing reasons, we conclude that Petitioner has not established a reasonable likelihood of prevailing on its assertion that any of claims 1–4 of the '342 patent are unpatentable.

IV. ORDER

In consideration of the foregoing, it is hereby ORDERED that the Petition is *denied*.

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