

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SHANGHAI HONGENE BIOTECH CORP.,
Petitioner,

v.

CHEMGENES CORP.,
Patent Owner.

IPR2023-00862
Patent 8,541,569 B2

Before JOHN G. NEW, ZHENYU YANG, and CYNTHIA M. HARDMAN,
Administrative Patent Judges.

YANG, *Administrative Patent Judge.*

PRELIMINARY GUIDANCE
PATENT OWNER'S MOTION TO AMEND

I. INTRODUCTION

On October 24, 2023, we instituted trial as to claims 1 and 2 of U.S. Patent No. 8,541,569 B2. Paper 6. After institution, Patent Owner filed a Motion to Amend. Paper 11 (“Motion” or “Mot.”). In its Motion, Patent Owner proposes to amend the ’569 patent to replace claims 1 and 2 with substitute claims 33 and 34. Mot. 1–2. Petitioner filed an Opposition to Patent Owner’s Motion. Paper 13 (“Opposition” or “Opp.”).

In the Motion, Patent Owner requested that we provide preliminary guidance concerning the Motion in accordance with the Board’s Pilot Program concerning motion to amend practice and procedures. Mot. 1; *see also* Notice Regarding a New Pilot Program Concerning Motion to Amend Practice and Procedures in Trial Proceedings under the America Invents Act before the Patent Trial and Appeal Board, 84 Fed. Reg. 9,497 (Mar. 15, 2019) (providing a patent owner with the option to receive preliminary guidance from the Board on its motion to amend) (“Notice”). We have considered Patent Owner’s Motion and Petitioner’s Opposition.

In this Preliminary Guidance, we provide information indicating our initial, preliminary, and non-binding views on whether Patent Owner has shown a reasonable likelihood that it has satisfied the statutory and regulatory requirements associated with filing a motion to amend in an *inter partes* review and whether Petitioner (or the record) establishes a reasonable likelihood that the substitute claims are unpatentable. *See* Notice, 84 Fed. Reg. at 9,497 (“The preliminary guidance . . . provides preliminary, non-binding guidance from the Board to the parties about the [motion to amend]”); *see also* 35 U.S.C. § 316(d) (statutory requirements for a motion to amend); 37 C.F.R. § 42.121 (regulatory requirements and burdens for a motion to amend); *Lectrosonics, Inc. v Zaxcom, Inc.*,

IPR2018-01129, Paper 15 (PTAB Feb. 25, 2019) (precedential) (providing information and guidance regarding motions to amend).

For purposes of this Preliminary Guidance, we focus on the proposed substitute claims, and specifically on the amendments proposed in the Motion. *See* Notice, 84 Fed. Reg. at 9,497. We do not address the patentability of the originally challenged claims. *Id.* Moreover, in formulating our preliminary views on the Motion and Opposition, we have not considered the parties' other substantive papers on the underlying merits of Petitioner's challenges. We emphasize that the views expressed in this Preliminary Guidance are subject to change upon consideration of the complete record, including any revision to the Motion filed by Patent Owner. Thus, this Preliminary Guidance is not binding on the Board when rendering a final written decision. *See id.* at 9,500.

II. PRELIMINARY GUIDANCE

As a threshold matter, Patent Owner has not clearly articulated whether the Motion is either: (1) contingent upon a finding in a final written decision that the challenged claims are unpatentable; or (2) non-contingent. "A motion to amend claims may cancel claims and/or propose substitute claims." *Lectrosonics* at 3 (citing 35 U.S.C. § 316(d)(1); 37 C.F.R. § 42.121(a)(3)). A request to substitute claims ordinarily will be treated as contingent. *Id.* "In other words, a proposed substitute claim normally will be considered only if a preponderance of the evidence establishes that the original patent claim that it replaces is unpatentable." *Id.* A patent owner should adopt a claim-by-claim approach to specifying the contingency of substitution, e.g., which claim is to be substituted for which claim, and under what circumstances. *Id.*

For purposes of this Preliminary Guidance, we treat the Motion as contingent upon a finding in a final written decision that the challenged claims are unpatentable. *Lectrosonics* at 3 (“[A] request to substitute claims ordinarily will be treated as contingent”). However, we advise Patent Owner to expressly state whether the motion is contingent or non-contingent in either a reply in support of the motion to amend or in a revised motion to amend.

A. Statutory and Regulatory Requirements

For the reasons discussed below, at this stage of the proceeding, and based on the current record, it appears that Patent Owner has not shown a reasonable likelihood that it has satisfied the statutory and regulatory requirements associated with filing a motion to amend.

1. Reasonable Number of Substitute Claims

Does Patent Owner propose a reasonable number of substitute claims? (35 U.S.C. § 316(d)(1)(B))
Yes. Patent Owner proposes no more than one substitute claim for each challenged claim. Mot. 2, A1–A13 (Appx. A). Petitioner does not argue otherwise.

2. Respond to Ground of Unpatentability

Does the Motion respond to a ground of unpatentability involved in the trial? (37 C.F.R. § 42.121(a)(2)(i))
Yes. It appears that the Motion responds to the grounds of unpatentability. Mot. 15–23. Petitioner does not argue otherwise.

3. Scope of Amended Claims

Does the amendment seek to enlarge the scope of the claims? (35 U.S.C. § 316(d)(3); 37 C.F.R. § 42.121(a)(2)(ii))

No. It appears that each proposed substitute claim is narrower in scope than the corresponding original claim. Mot. 3–5, A1–A13 (Appx. A). Petitioner does not argue otherwise.

4. New Matter

Does the amendment seek to add new subject matter? (35 U.S.C. § 316(d)(3); 37 C.F.R. § 42.121(a)(2)(ii))

Yes. For the reasons discussed below, on this record, we find that Patent Owner has not shown a reasonable likelihood that the substitute claims introduce no new matter relative to the original disclosure.

Patent Owner asserts that the proposed substitute claims are supported by the specification of the original application, No. 12/708,827 (“the ’827 application”). Mot. 5. Patent Owner states that the ’827 application is a continuation-in-part of International Application PCT/US2009/005063 and claims priority to U.S. Provisional Application No. 61/191,065; however, Patent Owner does not identify support for the proposed substitute claims in these applications because “Patent Owner does not currently seek the benefit of the filing date of the disclosure set forth in the earlier-filed PCT/US2009/005063 Application or in the earlier-filed ’065 Provisional Application.” *Id.*

Patent Owner asserts that proposed substitute claim 33 is supported by stating that “[e]ach of these elements is recited in original Claim 1 of the ’569 Patent (Ex. 1001, 111:21-114:34), and is supported by, *inter alia*, pages 3:10-7:17, 14:22-19:4, 33:6-15, 118:1-122:11 (Claim 1), 126:5-9 (Claim 5) of the ’827 Application. Ex. 1002, 4:10-8:17, 15:23-20:4, 34:6-10, 119:1-123:11, 127:5-9; Ex. 2001, ¶75.” Mot. 10.

Patent Owner asserts that proposed substitute claim 34 is supported by stating that “[e]ach of these elements is recited in original Claim 2 of the ’569 Patent (Ex. 1001, 114:34-117:52), and is supported by, *inter alia*, pages 7:19-10:23, 33:6-10, 99:20-100:4, 122:13-125:23 (Claim 2), 126:5-9 (Claim 5) of the ’827 Application. Ex. 1002, 8:19-11:23, 34:6-10,

100:20-101:4, 123:13-126:23, 127:5-9. Ex. 2001, ¶83.” Mot. 14–15. Patent Owner contends proposed substitute claim 34 does not present new matter because Patent Owner is claiming less than it has a right to claim because

[t]he ’827 Application discloses and supports many alternative nucleoside bases including, *inter alia*, where Bⁿ is thymine (6:17; 18:2; 31:3; 40:15; 51:24), N²-isobutyl guanine (55:9-16; 59:1 (structure ix); 111:6; 113:1), N⁴-benzoyl 5-methyl cytosine (52:9-10; 54:25-55:1; 69:10 (structure 1), N⁴-benzoyl cytosine (55:9-16; 68:16-17), N⁶-benzoyl adenine (6:7; 17:21; 30:25), and uracil (51:23-24). Ex. 1002, 7:17; 19:2; 32:3; 41:15; 52:24; 56:9-16; 60:1 (structure ix); 112:6; 114:1; 53:9-10; 55:25-56:2; 70:10 (structure 1); 56:9-16; 69:16-17; 7:7; 18:21; 31:25; 52:23-24; Ex. 2001, ¶84.

Id. at 15.

Petitioner argues Patent Owner does not properly identify support for proposed substitute claims 33 and 34 because the Motion merely provides string citations. Opp. 1–5. According to Petitioner, “a motion to amend must ‘*describe how* the original disclosure of the patent and any relied upon prior application supports each claim that is added or amended.’ . . . This burden of production is not satisfied by merely string citing parts of the priority document.” *Id.* at 2 (emphasis in original, citations omitted).

More specifically, Petitioner contends Patent Owner’s identification of support for proposed substitute claim 33 is insufficient because the Motion does not specify how each limitation is supported, and “merely has a table reciting the claim as a whole, then a single paragraph containing only the conclusory and vague assertion that the claim elements are ‘supported by’ string citations to the ’827 Application.” Opp. 3.

Moreover, Petitioner contends Patent Owner’s identification of support for proposed substitute claim 34 is insufficient because it repeats “the deficient approach for Substitute Claim 33, but adds a paragraph regarding the exceptionally broad claim limitation permitting ‘Bⁿ’ to be hydrogen or *any nucleobase* except for six specific recited nucleobases and twelve specific compounds, which are expressly carved out from the scope of the claim.” Opp. 3–4 (emphasis in original). Petitioner argues that the Motion merely states that the ’827 application discloses many alternative

nucleoside bases, but does not specify how many or which bases are disclosed, or “explain how such a disclosure could support the vast array of nucleobases encompassed by Bⁿ.” *Id.* Petitioner contends the Motion also includes a string citation “in which the only ‘explanation’ provided appears intended to support the six bases expressly carved-out from the scope of Bⁿ,” which is insufficient because “a disclosure of bases that are outside the scope of the claims cannot be support for bases encompassed by Bⁿ.” *Id.* (emphasis omitted).

On this record, we agree with Petitioner that the string cites in Patent Owner’s Motion do not explain how each individual claim limitation is supported. Patent Owner provides only bare citations, leaving it to the Board to discern how and which citation purportedly supports each claim limitation.

We also agree with Petitioner’s position that Patent Owner’s citations do not adequately support claim 34’s limitation reciting options for Bⁿ because the claim limitation results in a very large genus of potential nucleobases that Patent Owner has not shown is disclosed in the specification. On this record, it also appears that Patent Owner has not shown that a person of ordinary skill in the art would have immediately envisaged or recognized the full genus of nucleobases in proposed substitute claim 34. Thus, it is our preliminary and non-binding view that Patent Owner has not shown a reasonable likelihood that the proposed substitute claims add no new matter.

We emphasize that our position on written description is preliminary, and invite the parties to address this issue in further briefing and/or in a revised motion to amend.

B. Patentability¹

For the reasons discussed below, at this stage of the proceeding, and based upon the current record,² it appears that Petitioner has shown a reasonable likelihood that proposed substitute claims 33 and 34 are unpatentable.

Does the record establish a reasonable likelihood that the proposed substitute claims are unpatentable?

Yes. On this record, it appears that Petitioner has shown a reasonable likelihood that proposed substitute claims 33 and 34 are unpatentable as obvious on the grounds discussed below.

We note that Patent Owner has not yet had an opportunity to respond to the arguments and evidence cited in Petitioner's Opposition or this Preliminary Guidance. Patent Owner will have the opportunity to do so in a Reply or in a Revised Motion to Amend in this proceeding.

Proposed Substitute Claims 33 and 34

In proposed substitute claim 33, Patent Owner proposes "delet[ing] the species in Claim 1 that Petitioner alleged [were] anticipated in Ground I," and "remov[ing] compounds from Claim 1's Markush Groups (where Bⁿ is, thymine and 5-(C₁)alkyluracil) . . . based on prior sales of those compounds." Mot. 16.

In proposed substitute claim 34, Patent Owner proposes "delet[ing] the species in Claim 2 that Petitioner alleged [were] anticipated in Ground II," and "remov[ing] certain compounds (where Bⁿ is not thymine, N²-isobutyryl guanine, N⁴-benzoyl 5-methyl cytosine, N⁴-benzoyl cytosine, N⁶-benzoyl adenine, or uracil), based on prior sales of those compounds." *Id.*

¹ Unless otherwise noted, all citations to the prior art references are to the original page numbers of the references themselves.

² We express no view on the patentability of original claims 1 and 2 in this Preliminary Guidance. Instead, we focus on the proposed amendments to those claims in the Patent Owner's Motion to Amend.

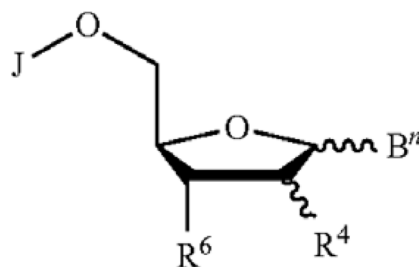
We discuss below our preliminary views regarding the proposed amendments in the context of the prior art Petitioner raises in its Opposition.

I. Anticipation

For the reasons discussed below, it appears that Petitioner has not established a reasonable likelihood that proposed substitute claims 33 and 34 are anticipated.

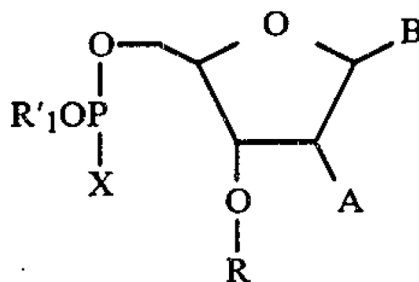
A. U.S. Patent No. 4,668,777 (“the ’777 patent”)³

Petitioner argues the ’777 patent discloses a large genus of compounds that significantly overlaps with the large genus of proposed substitute claims 33 and 34. Opp. 7–11. Petitioner maps the ’777 patent’s claim 1 compound to the limitations of Formula Ia of proposed substitute claims 33 and 34. *Id.* (citing Ex. 1010, 4:28–32, 4:34–44, 19:15–30, 19:39–42; Ex. 1005 ¶¶ 35–36, 38–40, 42–47, 49–57). Formula Ia of the proposed substitute claims is depicted below.



Mot. A-1.

The ’777 patent’s claim 1 compound is depicted below:



Ex. 1010, 19:14–42.

Petitioner contends “the ’777 patent discloses preferences for substituents at the 1’-position, 2’-position, 3’-position, and 5’-position that fall within the scope of Substitute Claims 33 and 34 of the ’569 Patent.” Opp. 7–11.

³ U.S. Patent 4,668,777, issued May 26, 1987 (Ex. 1010).

Petitioner argues that a person of ordinary skill in the art “reviewing the ’777 Patent would immediately envisage many individual 5’-phosphoramidite compounds within the scope of Substitute Claims 33 and 34” because (1) “[c]laim 1 of the ’777 Patent has the identical core 5’-phosphoramidite structure” as the proposed substitute claims; (2) “[t]he variable substituents described in claim 1 of the ’777 Patent significantly overlap with the corresponding substituents” of the proposed substitute claims; and (3) “the ’777 Patent provides specific preferences and examples that guide a POSA to a substantially smaller subgenus of 5’-phosphoramidites with specifically identifiable members that fall within the scope” of the proposed substitute claims. *Id.* at 10–11 (citing Ex. 1005 ¶ 55).

i. 1’-position

Petitioner argues that “the ’777 Patent specifically discloses one claimed variation for B” in proposed substitute Claim 33, namely hypoxanthine, because the ’777 patent defines “B” as a “nucleoside or deoxynucleoside base” in claim 1 and “highlights ‘adenine, hypoxanthine, guanine, cytosine, uracil, and thymine.’” Opp. 8 (emphasis omitted, citing Ex. 1010, 4:28–32, 19:25; Ex. 1005 ¶¶ 38–39).

Petitioner also argues that the ’777 Patent discloses “multiple claimed variations for B” in proposed substitute Claim 34, namely adenine, hypoxanthine, guanine, and cytosine, because the ’777 patent defines “B” as a “nucleoside or deoxynucleoside base” in claim 1 and “highlights ‘adenine, hypoxanthine, guanine, cytosine, uracil, and thymine.’” Opp. 8 (citing Ex. 1010, 4:28–32, 19:25; Ex. 1005 ¶¶ 38, 40) (emphasis omitted). According to Petitioner, proposed substitute claim 34 does not exclude adenine, hypoxanthine, guanine, and cytosine from the scope of B”. *Id.* (citing Ex. 1005 ¶ 40).

ii. 2’-position

Petitioner argues that “the ’777 Patent specifically discloses multiple claimed variations for R⁴” in proposed substitute claims 33 and 34 because the ’777 patent defines “A” as “H, OH, or OR₄ in which R₄ is a blocking group” in claim 1 and “discloses that ‘[t]he blocking groups represented by R₄ in the above formulae include trityl, methoxytrityl, dimethoxytrityl, dialkylphosphite, pivalyl, isobutyloxycarbonyl, t-butyl dimethylsilyl, acetyl and similar such blocking groups.’” Opp. 8–9 (citing Ex. 1010, 4:34–37, 19:25–26; Ex. 1005 ¶¶ 42, 46). According to Petitioner, a person of ordinary skill in the art “would have understood that these blocking groups were

conventional groups for protecting the 2'-oxygen, most of which are within the scope of the R⁴ group" of proposed substitute claims 33 and 34. *Id.* at 8 (citing Ex. 1005 ¶ 43). Petitioner provides examples from the '777 patent in which A is OR₄ and R₄ is acetyl, trityl, methoxytrityl, dimethoxytrityl, or t-butyl dimethylsilyl. *Id.* at 8–9 (citing Ex. 1005 ¶¶ 43–45).

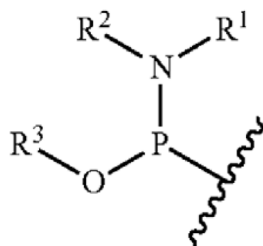
Petitioner argues that when R⁴ is acetyl in the '777 patent, the compound "is within the scope of R⁴ for Substitute Claims 33 and 34 when R⁴ is —OC(=O)R¹² and R¹² is a C₁ alkyl group (CH₃).” Opp. 8–9 (citing Ex. 1005 ¶ 43). Petitioner argues that when R⁴ is trityl, methoxytrityl, or dimethoxytrityl in the '777 patent, the compound "is within the scope of R⁴ for Substitute Claims 33 and 34 when R⁴ is R⁵, which in turn is a substituted or unsubstituted phenyl group (trityl, methoxytrityl, or dimethoxytrityl) with an intervening oxygen atom attached to the 2'-position of the ring.” *Id.* at 9 (citing Ex. 1005 ¶ 44). Petitioner contends that when R⁴ is t-butyl dimethylsilyl in the '777 patent, the compound "is within the scope of R⁴ for Substitute Claim 33 when R⁴ is O—Si(R¹¹)₃, two R¹¹ groups are methyl, and one is t-butyl.” *Id.* (citing Ex. 1005 ¶ 45).

iii. 3'-position

Petitioner argues that the '777 patent discloses triarylmethyl compounds that satisfy proposed substitute claim 33 "where 'Z' is a 'substituted or unsubstituted triarylmethyl group[]" because "[c]laim 1 of the '777 Patent requires that 'R' is 'a triarylmethyl blocking group selected from' a group of three specific compounds.” Opp. 9 (citing Ex. 1010, 19:32–42; Ex. 1005 ¶ 47).

iv. 5'-position

Petitioner argues that "[t]he positions of the R'₂ and R'₃ groups in the '777 Patent correspond to the positions of R¹ and R² groups when 'J' is the structure in the '569 Patent," as shown below. Opp. 9 (citing Ex. 1005 ¶ 50).



Mot. A-1.

Petitioner contends “[c]laim 1 of the ’777 Patent provides that when R² and R³ are separate, they can be ‘alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl containing up to 10 carbon atoms.’” Opp. 9–10 (citing Ex. 1010, 19:28–30; Ex. 1005 ¶ 51). According to Petitioner, this disclosure in the ’777 patent “overlaps to a large degree” with the requirement in R¹ and R² of proposed substitute claims 33 and 34 “which can be ‘a substituted or unsubstituted (C₁-C₁₂) alkyl group’ or ‘a substituted or unsubstituted (C₃-C₂₀) cycloalkyl group”” because both the ’777 patent and proposed substitute claim 33 “embrace alkyl groups containing up to ten carbons and cycloalkyl groups containing up to ten carbons.” *Id.* at 10 (citing Ex. 1005 ¶¶ 51–52).

Petitioner also contends “[t]he position of the R¹ group in the ’777 Patent corresponds to R³ in the ‘J’ group” of proposed substitute claims 33 and 34. Opp. 10 (citing Ex. 1005 ¶ 53). Petitioner states that the proposed substitute claims defines R₃ as “a phosphate protecting group.” *Id.* (citing Ex. 1005 ¶ 49). Petitioner argues that the ’777 patent defines R¹ as “a hydrocarbyl radical containing up to 10 carbon atoms” in claim 1 and “discloses that R₁ can include ‘alkyl, alkenyl, aryl, aralkyl and cycloalkyl containing up to about 10 carbon atoms,’ and that two ‘especially’ preferred options are ‘methyl and ethyl.’” *Id.* (citing Ex. 1010, 4:38–44, 19:26–27; Ex. 1005 ¶ 53). According to Petitioner, “[m]ethyl and ethyl are well-known phosphate protecting groups, as reflected in their use and preference as such in the ’777 Patent.” *Id.* (citing Ex. 1005 ¶ 54).

Based on the current record, Petitioner’s arguments are not persuasive. “[U]nless a prior art reference discloses within the four corners of the document not only all of the limitations claimed but also all of the limitations arranged or combined in the same way as recited in the claim, it cannot be said to prove prior invention of the thing claimed and, thus, cannot anticipate under 35 U.S.C. § 102.” *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1371 (Fed. Cir. 2008). Petitioner does not argue that the ’777 patent discloses a compound with all the substituents at the 1’-position, 2’-position, 3’-position, and 5’-position, arranged or combined in the same way as recited in proposed substitute claims 33 and 34.

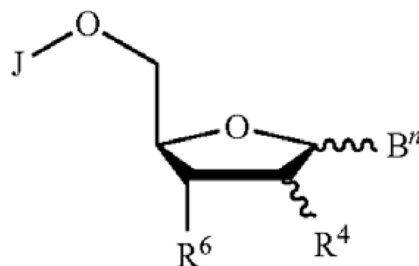
We recognize that a reference can anticipate a claim “even if it does not expressly spell out all the limitations arranged or combined as in the claim, if a person of skill in the art, reading the reference, would at once envisage the claimed arrangement or combination.” *Microsoft Corp. v. Biscotti, Inc.*, 878 F.3d 1052, 1068 (Fed. Cir. 2017) (quotation marks and brackets omitted). Petitioner’s contentions, however, require picking and choosing from

the '777 patent. As Petitioner acknowledges, the '777 patent discloses a large genus of compounds (Opp. 7), and we are not persuaded that an ordinarily skilled artisan would at once envisage the arrangement or combination as recited in proposed substitute claims 33 and 34.

Thus, it is our preliminary, non-binding opinion that Petitioner has not established a reasonable likelihood that the '777 patent anticipates proposed substitute claims 33 and 34.

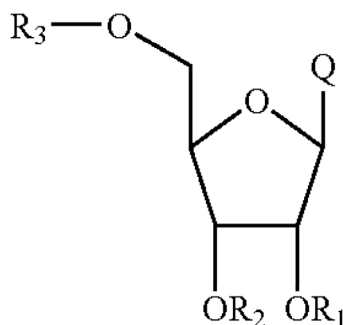
*B. U.S. Patent App. Pub. No. 2008/0234475 A1
("the '475 publication")⁴*

Petitioner argues the '475 publication discloses a large genus of compounds that significantly overlaps with the large genus of proposed substitute claim 33. Opp. 12–16. Petitioner maps the '475 publication's claim 3, formula I compound to the limitations of Formula Ia of proposed substitute claims 33 and 34. *Id.* (citing Ex. 1011 ¶¶ 17, 20, 73–74, claim 3; Ex. 1005 ¶¶ 61–71). Formula Ia of the proposed substitute claims is depicted below.



Mot. A-1.

The '475 publication's claim 3, formula I compound is depicted below:



Ex. 1011, claim 3.

⁴ U.S. Patent App. Pub. 2008/0234475 A1, published September 25, 2008 (Ex. 1011).

Petitioner contends “the ’475 Publication discloses preferences for substituents at the 1’-position, 2’-position, 3’-position, and 5’-position that fall within the scope of Substitute Claims 33 and 34 of the ’569 Patent.”

Opp. 13–16. Petitioner argues that a person of ordinary skill in the art “reviewing the ’475 Publication would immediately envisage many individual 5’-hydroxyl compounds within the scope of Substitute Claims 33 and 34” because (1) “[c]laim 3 of the ’475 Publication has the identical core 5’-hydroxyl structure” as the proposed substitute claims; (2) “[t]he variable substituents described in claim 3 of the ’475 Publication significantly overlap with the corresponding substituents” of the proposed substitute claims; and (3) “the ’475 Publication provides specific preferences and examples that guide a POSA to a substantially smaller subgenus of 5’-hydroxyl compounds with specifically-identifiable members that fall within the scope” of the proposed substitute claims. *Id.* at 15–16 (citing Ex. 1005 ¶ 69).

i. 1’-position

Petitioner argues that the ’475 Publication discloses that the purine (Q) can be hypoxanthine, 2-aminoadenine, and “8-halo, amino, thiol, thioalkyl, hydroxyl and other 8-substituted adenines and guanines.” Opp. 13–14 (citing Ex. 1011 ¶¶ 17, 73–74; Ex. 1005 ¶¶ 63–65). According to Petitioner, each of these options is within the scope of B” in proposed substitute claim 34, and proposed substitute claim 33 lists hypoxanthine, 2-aminopurine, 8-bromoguanine, 8-aminoguanine, 8-bromopurine, and 8-aminopurine as options for B”. *Id.* (citing Ex. 1005 ¶¶ 63–65).

Petitioner contends that a person of ordinary skill in the art “would have understood that 2-aminoadenine is an example of a 2-aminopurine.” *Id.* (citing Ex. 1005 ¶ 64). Petitioner also contends that a person of ordinary skill in the art would have understood that 8-halo adenines and guanines include 8-bromopurine, an exemplary 8-halo guanine is 8-bromoguanine, and 8-amino adenines and guanines are 8-aminopurines and include 8-aminoguanine. *Id.* at 14 (citing Ex. 1005 ¶ 65).

ii. 2’-position

Petitioner argues that “[t]he ’475 Publication discloses that R₁ in OR₁ is substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl, or substituted or unsubstituted C₂-C₁₂ alkynyl.” Opp. 14 (citing Ex. 1011, claim 3; Ex. 1005 ¶ 66). According to Petitioner, “[t]his tracks the limitations of Substitute Claims 33 and 34 where R⁴ is R⁵, and R⁵ has an intervening oxygen atom at the 2’-position bound to “a substituted or

unsubstituted (C₁-C₁₂)alkyl group, a substituted or unsubstituted (C₂-C₁₂)alkenyl group, [or] a substituted or unsubstituted (C₂-C₁₂)alkynyl group’.” *Id.* at 14–15 (citing Ex. 1005 ¶ 66).

iii. 3’-position

Petitioner argues that the ’475 publication discloses hydroxyl protecting group examples that satisfy the proposed substitute claims “which permit[s] R⁶ to be –O–Z, where Z includes ‘an unsubstituted or substituted trityl group’ and ‘an unsubstituted or substituted tetrahydropyranyl group’” because “[t]he ’475 Publication discloses that the R₂ in OR₂ can be either hydrogen or ‘a hydroxyl protecting group,’ such as a triphenylmethyl (trityl) group, a tetrahydropyranyl group, or a 9-phenylxanthyl. Opp. 15 (citing Ex. 1011 ¶ 20; Ex. 1005 ¶ 67). More specifically, Petitioner argues that the ’475 publication discloses that “the hydroxyl protecting group can be ‘dimethoxytrityl (DMT)’ or ‘9-phenylxanthine-9-yl (Pixyl),” which are a substituted trityl and a 9-phenylxanthyl, respectively. *Id.* (citing Ex. 1011 ¶ 20; Ex. 1005 ¶ 67).

iv. 5’-position

Petitioner argues that “[t]he ’475 Publication discloses that R₃ in OR₃ can be either hydrogen or a hydroxyl protecting group” such that “[w]hen R₃ is hydrogen, this meets Substitute Claims 33 and 34 where J is H.” Opp. 15 (citing Ex. 1011 claim 3; Ex. 1005 ¶ 68).

Based on the current record, Petitioner’s arguments are not persuasive. Similar to our reasoning in discussing anticipation by the ’777 patent above, Petitioner does not argue that the ’475 publication discloses a compound with all the substituents at the relevant positions, arranged or combined in the same way as recited in the proposed substitute claims. Additionally, given the picking and choosing from the options disclosed in the ’475 publication needed to arrive at the genus recited in the proposed substitute claims, Petitioner does not show sufficiently that an ordinarily skilled artisan would at once envisage the arrangement or combination as recited in proposed substitute claims.

Thus, it is our preliminary, non-binding opinion that Petitioner has not established a reasonable likelihood that the ’475 publication anticipates proposed substitute claims 33 and 34.

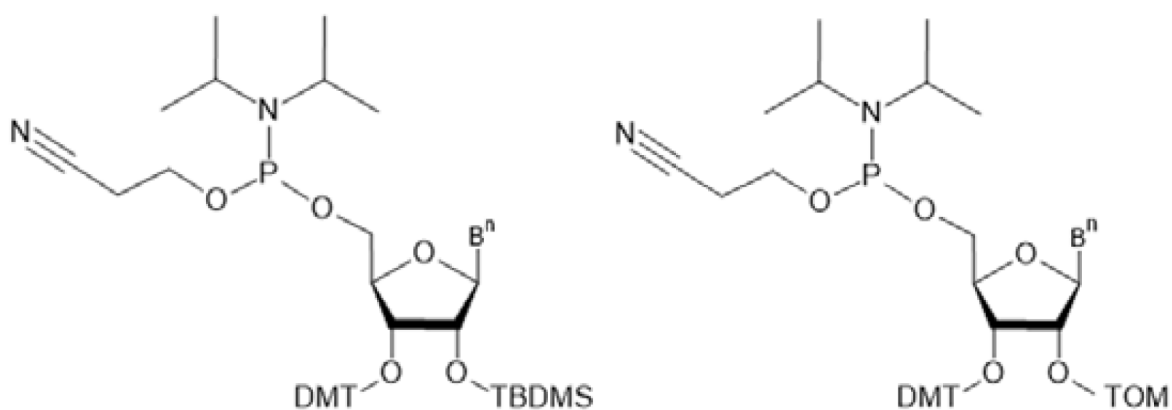
II. Obviousness

For the reasons discussed below, it appears that Petitioner has established a reasonable likelihood that proposed substitute claims 33 and 34 would have been obvious.

A. Srivastava⁵ in View of the Knowledge of a Person of Ordinary Skill in the Art

Petitioner argues that the proposed substitute claims would have been obvious over Srivastava in view of the knowledge of a person of ordinary skill in the art as shown by the 1999 ChemGenes Catalog,⁶ Manoharan,⁷ Ramzaeva,⁸ Kawasaki,⁹ and Oberhauser.¹⁰ Opp. 17 (citing Ex. 1005 ¶¶ 75, 82–98).

According to Petitioner, proposed substitute claim 33 includes the structures reproduced below with two different groups (TBDMS and TOM) at the 2'-position and varying Bⁿ groups.

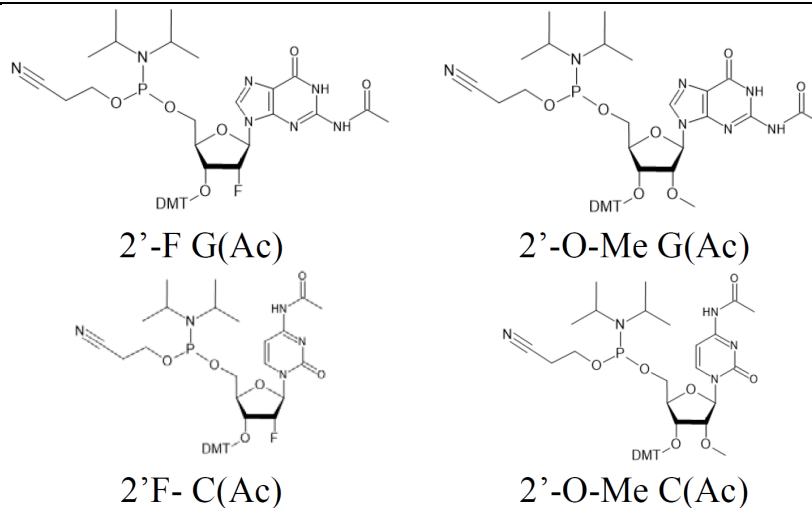


Opp. 17 (citing Ex. 1005 ¶¶ 76–78).

In addition, according to Petitioner, proposed substitute claim 34 includes the structures reproduced below with two different exemplary groups at the 2'-position (fluoro and O-methyl) and acetyl-protected cytosine and guanine groups.

⁵ Srivastava et al., *RNA synthesis: phosphoramidites for RNA synthesis in the reverse direction. Highly efficient synthesis and application to convenient introduction of ligands, chromophores and modifications of synthetic RNA at the 3'-end.*, NUCLEIC ACIDS SYMPOSIUM SERIES No. 52, 103–104 (2008) (Ex. 1012).

⁶ ChemGenes Corporation, *Bio technology products & manufacturer of DNA-RNA intermediates* (1999) (Ex. 2010).



Opp. 23 (citing Ex. 1005 ¶¶ 106–109).

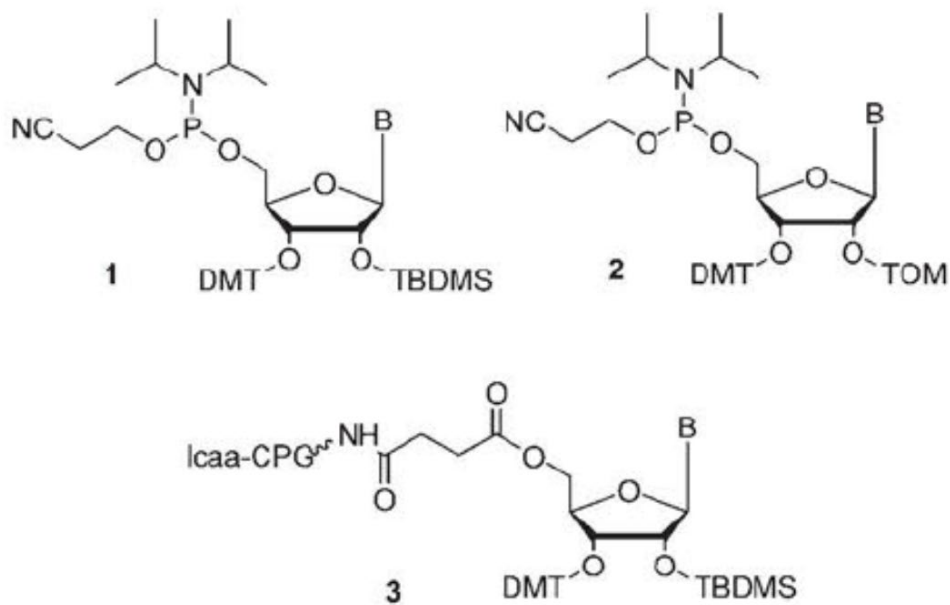
⁷ Manoharan, *RNA interference and chemically modified small interfering RNAs*, 8 CURRENT OP. IN CHEM. BIO. 570–79 (2004) (Ex. 1016).

⁸ Ramzaeva et al., 123. 7-Deazaguanine DNA: oligonucleotides with hydrophobic or cationic side chains, 80 HELVETICA CHIMICA ACTA 1809–22 (1997) (Ex. 1019).

⁹ Kawasaki et al., *Uniformly modified 2'-deoxy:2'-fluoro phosphorothioate oligonucleotides as nuclease-resistant antisense compounds with high affinity and specificity for RNA targets*, 36(7) J. MED. CHEM. 831–41 (1993) (Ex. 1022).

¹⁰ Oberhauser et al., *Effective incorporation of 2'-O-methyl-oligoribonucleotides into liposomes and enhanced cell association through modification with thiocholesterol*, 20(3) NUCLEIC ACIDS RES. 533–38 (1992) (Ex. 1023).

Petitioner relies on Srivastava's Figure 1, structures 1 and 2 for its obviousness arguments. Srivastava's Figure 1 is reproduced below.



Where B = A (N-Bz), C (N-Bz), C (N-Ac), G (N-Ac), U.

Figure 1. Structures of reverse phosphoramidites and solid supports.

Ex. 1012, 104.

Petitioner contends that “Srivastava discloses that structures 1 and 2 are ‘reverse RNA monomer phosphoramidites for RNA synthesis in [the] 5′→3′-direction’ that ‘lead to very clean oligonucleotide synthesis allowing for introduction of various modifications at the 3′-end.’” Opp. 18 (citing Ex. 1012, 103; Ex. 1005 ¶ 79).

Petitioner contends that “[t]he only difference between structures 1 and 2 in Srivastava and the two structures of Substitute Claim 33 above is the identity of the base group (B” in Substitute Claim 33).” Opp. 18 (citing Ex. 1005 ¶ 81). According to Petitioner, a person of ordinary skill in the art “would have understood that the five base groups (B) in [Srivastava’s] structures 1 and 2 were (1) N⁶-benzoyl-adenine, (2) N⁴-benzoyl-cytosine, (3) N⁴-acetyl-cytosine, (4) N²-acetyl-guanine, and (5) uracil.” *Id.* (citing Ex. 1005 ¶ 80).

Petitioner argues that a person of ordinary skill in the art would have been motivated to use modified base groups with Srivastava's Figure 1, structures 1 and 2 because a person of ordinary skill in the art "would have understood that conventional RNA synthesis in the 3' → 5' direction often employed modified base groups, such as those in Substitute Claim 33." *Id.* at 19 (citing Ex. 1005 ¶ 82). Petitioner also argues that a person of ordinary skill in the art would have been motivated to use modified base groups with Srivastava's Figure 1, structures 1 and 2 for reverse RNA synthesis in the 5' → 3' direction, "[g]iven the 'vast number of applications' for the reverse RNA phosphoramidites disclosed in Srivastava" and "to have a complementary library of phosphoramidite reagents." *Id.* (citing Ex. 1005 ¶¶ 82, 84).

Petitioner contends a person of ordinary skill in the art would have had a reasonable expectation of success, including in using such phosphoramidites in oligonucleotide synthesis in the 5' → 3' direction, because "[t]he synthesis of such base groups and reverse phosphoramidites in general were known, and the synthetic process would have involved routine chemistry" for a person of ordinary skill in the art, and "Srivastava discloses that 'there is no difference in coupling efficiency during oligonucleotide synthesis using our reverse RNA monomers (for 5' → 3'-direction) as compared to standard 3'-CED phosphoramidites (for 3' → 5' direction).'" *Id.* at 21–22 (citing Ex. 1005 ¶¶ 96–97; Ex. 1012, 103).

Petitioner contends a person of ordinary skill in the art "would have known that phosphoramidites with various modified bases were commercially available and useful in scientific research," such as those included in the 1999 ChemGenes Catalog, Manoharan, and Ramzaeva. *Opp.* 19–22 (citing Ex. 1005 ¶¶ 85–87). More specifically, Petitioner contends a person of ordinary skill in the art would have been motivated to include the following bases:¹¹

- 7-deaza guanosine and 7-deaza adenosine based on the 1999 ChemGenes Catalog and Ramzaeva, which would result in compounds that meet Substitute Claim 33 where Bⁿ is 7-deazaadenine and 7-deazaguanine (*id.* at 20 (citing Ex. 2010, 56; Ex. 1019, 1809; Ex. 1005 ¶¶ 85–86, 89));
- N₃-methyl uridine, N₃-methyl thymidine, 5-methyl cytidine, and N-ethyl cytidine based on the 1999 ChemGenes Catalog, which would result in compounds that meet proposed substitute claim 33 where Bⁿ is N-3-(C₁-C₆)alkyluracil, N-3 methyl thymine, and 5-(C₁-C₆)alkylcytosine (*id.* (citing Ex. 2010, 57–59; Ex. 1005 ¶¶ 85, 90));

- isomers of standard bases (such as isoguanosine and isocytidine) based on the 1999 ChemGenes Catalog, which are recited in proposed substitute claim 33 (*id.* (citing Ex. 2010, 58, 61; Ex. 1005 ¶¶ 85, 91));
- inosine (a hypoxanthine group attached to a ribose ring) based on the 1999 ChemGenes Catalog, which would result in a compound that meets proposed substitute claim 33 where Bⁿ is hypoxanthine (*id.* at 21 (citing Ex. 2010, 59; Ex. 1005 ¶¶ 85, 92));
- N3-thiobenzoyl ethyl uridine and 4-thiocyanoethyl uridine based on the 1999 ChemGenes Catalog, which would result in compounds that meet proposed substitute claim 33 where Bⁿ is N3-thiobenzoyl ethyl uracil and 4-thiouracil (*id.* (citing Ex. 2010, 58, 60; Ex. 1005 ¶¶ 85, 93)); and
- 2-aminopurine and 2,6-diaminopurine based on the 1999 ChemGenes Catalog, which are recited in proposed substitute claim 33 (*id.* (citing Ex. 2010, 61; Ex. 1005 ¶¶ 85, 94)).

For proposed claim 34, Petitioner contends “[t]he only difference between the N⁴-acetyl-cytosine and N²-acetyl-guanine structures 1 and 2 in Srivastava and the structures of Substitute Claim 34 above is the identity of the 2′-substituent.” Opp. 24 (citing Ex. 1005 ¶ 111). According to Petitioner, a person of ordinary skill in the art “would have been motivated to employ conventional 2′-modifications to Srivastava’s N⁴-acetyl-cytosine and N²-acetyl-guanine structures for the same reasons as in Substitute Claim 33 above,” including by substituting the 2′ group in the N⁴-acetyl-cytosine and N²-acetyl-guanine bases from Srivastava with 2′-fluoro or 2′-O-methyl. *Id.* (citing Ex. 1005 ¶¶ 112–13). Petitioner argues that “[t]he resulting compounds would meet the limitations of Substitute Claim 34 where R⁴ is halo (i.e., fluoro) or R⁵ (a C₁ alkyl group with an intervening oxygen atom).” *Id.* (citing Ex. 1005 ¶ 114).

¹¹ According to Petitioner, the 1999 ChemGenes Catalog and Manoharan also show that a person of ordinary skill in the art would have been motivated to include bases such as 5-iodo-cytidine, 5-iodo uridine, 5-bromo uridine, 5-bromo cytidine, 5-fluoro uridine, and 8-bromo adenosine, which would result in compounds that “meet Substitute Claim 33 where Bⁿ is 5-iodo-cytidine, 5-iodo uridine, 5-bromo uridine, 5-bromo cytidine, 5-fluoro uridine, and 8-bromo adenosine.” Opp. 19–20 (citing Ex. 2010, 56–62; Ex. 1016, 577; Ex. 1005 ¶¶ 85, 88). Proposed substitute claim 33, however, does not appear to include these bases in the list of options for Bⁿ.

For the additional options for R⁴ recited in proposed substitute claim 33, such as fluoro (R⁴ is halo) and O-methyl (R⁴ is R⁵, where R⁵ is a C₁ alkyl group with an intervening oxygen atom), Petitioner contends a person of ordinary skill in the art “would have been motivated to make each of these options with a reasonable expectation of success based on common knowledge alone” because a person of ordinary skill in the art “would have understood that 2′-fluoro modifications were a known technique to enhance binding affinity and selectivity for target RNA and stability toward nucleases” and that “2′-O-methyl groups were used in areas such as antisense research.” Opp. 22–23 (citing Ex. 1005 ¶ 98; Ex. 1022, 831; Ex. 1023, 533; Ex. 2010, 68–72).

For the additional options for R⁴ recited in proposed substitute claim 34, Petitioner contends a person of ordinary skill in the art “would have been motivated to use additional base groups with a reasonable expectation of success.” *Id.* at 24 (citing Ex. 1005 ¶ 117). According to Petitioner, “each of the modified base groups described above with respect to Substitute Claim 33 also meet[s] the B” limitation of Substitute Claim 34.” *Id.* (citing Ex. 1005 ¶ 117). Petitioner contends a person of ordinary skill in the art would have had a reasonable expectation of success “because the synthesis of such 2′-modifications and reverse phosphoramidites in general were known, and the synthetic process would have involved routine chemistry,” and for the same reasons discussed above. *Id.* at 25 (citing Ex. 1005 ¶¶ 115–16).

Petitioner contends there is no requirement to prove obviousness under the “lead compound” framework in this case because “[s]uch a framework is not consistent with how a [person of ordinary skill in the art] would have approached the selection of building blocks for oligonucleotide synthesis.” Opp. 25 (citing Ex. 1005 ¶¶ 99–104, 118). Petitioner argues that nevertheless, a person of ordinary skill in the art “would have been motivated to select structures 1 and 2 in Srivastava for the reasons provided above, including that Srivastava discloses that these compounds can be used in oligonucleotide[] synthesis, and these compounds are two of the few phosphoramidites specifically depicted in Srivastava.” *Id.*

Based on the current record, we find Petitioner’s contentions persuasive. Petitioner sufficiently describes the scope and content of Srivastava, and points out the differences between the proposed substitute claims and Srivastava. *See* Opp. 17–18, 23–24. Petitioner also persuasively argues that an ordinarily skilled artisan would have had a reason to (1) modify the base group of structures 1 and 2 in Srivastava, arriving at the subject matter of

proposed substitute claim 33, and (2) the 2'-substituent of structures 1 and 2 in Srivastava, arriving at the subject matter of proposed substitute claim 34, and would have had a reasonable expectation of success in doing so. *Id.* at 19–25. Thus, it is our preliminary, non-binding opinion that Petitioner has established a reasonable likelihood that Srivastava combined with the knowledge of a person of ordinary skill in the art as shown by the 1999 ChemGenes Catalog, Manoharan, Ramzaeva, Kawasaki, and Oberhauser would have rendered proposed substitute claims 33 and 34 obvious.

III. CONCLUSION

This concludes the Preliminary Guidance, which is Patent Owner's first option under the Board's Pilot Program. Notice, 84 Fed. Reg. at 9,497. Patent Owner has the additional option under the Board's Pilot Program to file a revised motion to amend by June 3, 2024 (Due Date 3). Paper 8, 2. These two options are in addition to Patent Owner's original option to file a reply brief in response to Petitioner's opposition to the motion to amend.

In addition to the two options under the Board's Pilot Program and the option to file a reply brief, Patent Owner is reminded that amendments of the challenged claims may also be pursued in a separate reissue or reexamination proceeding before, during, or after an AIA trial proceeding, including subsequent to the issuance of the Final Written Decision. We draw Patent Owner's attention to the April 2019 *Notice Regarding Options for Amendments by Patent Owner Through Reissue or Reexamination During a Pending AIA Trial Proceeding*. See 84 Fed. Reg. 16,654 (Apr. 22, 2019). If Patent Owner chooses to file a reissue application or a request for reexamination of the challenged patent, we remind Patent Owner of its continuing obligation to notify the Board of any such related matters in updated mandatory notices. See 37 C.F.R. § 42.8(a)(3), (b)(2).

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